American Heart Journal

VOL. 41 FEBRUARY, 1951 NO. 2

Original Communications

THE EFFECT OF DIGITOXIN ON THE APPARENT STROKE VOLUME, POSTEROANTERIOR CARDIAC DIAMETER, AND THE CARDIAC CYCLE IN NORMAL SUBJECTS AS STUDIED BY THE ELECTROKYMOGRAPH

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ALTHOUGH digitalis has been used in the treatment of congestive heart failure since the treatise of William Withering in 1785,[1] there is still confusion concerning the mechanism of action. There have been essentially 3 separate hypotheses advanced to define its action: (1) that digitalis increased the myocardial "tone,"[2-7] (2) that digitalis decreased the venous return to the heart,[8-12] and (3) that digitalis increased the strength of systolic contraction.[13-15] At present, probably more investigators favor the last explanation, although there are still observations which are difficult to include under a single theory.

A fundamental approach to the action of digitalis is the study of the effect of the drug on the phases of the cardiac cycle, which can be recorded serially in man by use of the electrokymograph.[16,17] The purpose of this paper is to record the changes in the phases of the cardiac cycle, posteroanterior cardiac diameters, and apparent stroke volume in normal subjects as the result of digitalis.

METHOD

The 12 subjects in this investigation were all normal male medical students. On the first day, the apparent stroke volumes and minute cardiac outputs were measured basal before breakfast, before lunch, and before the evening meal. All determinations were made with the subjects in the sitting position. They were allowed to carry on their routine day's activity; however, a period of 15 to 20 minutes of motionless sitting was observed just prior to the determination

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Received for publication Sept. 1, 1950.

*This work was done during the tenure of a Student Fellowship in Internal Medicine.

of the stroke volumes. Apparent stroke volume and minute cardiac output were estimated by use of the electrokymographic method outlined by Ring and co-workers[18] with certain modifications previously reported.[19] The first day established control values which were used in evaluating the changes following the administration of digitoxin. On the following morning, after a determination of the apparent cardiac output, 1 mg. of digitoxin was administered orally. The determinations were repeated before lunch, following which 0.6 mg. of digitoxin was administered. An additional 0.4 mg. of digitoxin was given following the determination of the cardiac output just prior to the evening meal, making a total of 2.0 mg. of digitoxin administered. The determinations were then made just prior to breakfast each day until the apparent stroke volume and the cardiac output had returned to the control value.

Border movements of the left ventricle and aortic knob were recorded during the control period and periodically following the administration of digitoxin until the termination of the experiment. Border tracings were obtained from the right ventricle and pulmonary artery on several subjects in addition to the left ventricle and the aortic knob in order to have simultaneous records of both right- and left-sided events.

The electrokymographic apparatus,* fluoroscopic apparatus, and method of recording the tracings have been previously described.[17,19] Blood pressures were determined with the use of an aneroid blood pressure cuff. The mean blood pressures were calculated by adding one-third of the pulse pressure to the diastolic blood pressure.[20] The peripheral resistance was determined by using the following formula:[21]

$$\text{PR} \quad \frac{\text{(dynes second)}}{\text{cm.}^5} = \frac{\text{mean blood pressure (mm. Hg)} \times 1332}{\text{cardiac output (milliliters per second)}}$$

The method by which the phases of the cardiac cycle were measured has been previously reported.[17]

RESULTS

The response to digitoxin in normal subjects may be classified as to effect on the minute cardiac output. The changes in cardiac output noted fell into 3 separate groups in the 12 subjects studied. Fig. 1,*A*, *B*, and *C*, illustrates the 3 types of response to digitoxin. The first type of response was characterized by a fall in minute cardiac output 4 hours after the administration of 1 mg. of digitoxin, which persisted 36 to 48 hours before returning to control values (Fig. 1,*A*). There were 2 of the 12 subjects in whom this type of response was noted. The second group was characterized by a fall in minute cardiac output 4 hours after the administration of digitoxin, followed by a rise to, or near, control levels 4 hours later. The cardiac output then fell again 24 to 36 hours after the initial administration of digitoxin, often to lower levels than that noted on the

*The electrokymograph with photomultiplier tube RCA No. 931-A used in this study was manufactured by the Cambridge Instrument Company, Inc., New York, N. Y. The recording device used was the Cambridge Simpli-Trol Electrocardiograph.

initial fall (Fig. 1,*B*). There were 5 of the 12 subjects in whom this type of response was noted. The third type of response was characterized by either a slight initial rise or no significant change in minute cardiac output, followed by a fall 24 to 48 hours after the administration of digitoxin (Fig. 1,*C*). There were 5 of the 12 subjects who demonstrated this type of response. Table I includes the apparent stroke volume, heart rate, minute cardiac output, blood pressure, mean blood pressure, and peripheral resistance in the 12 subjects

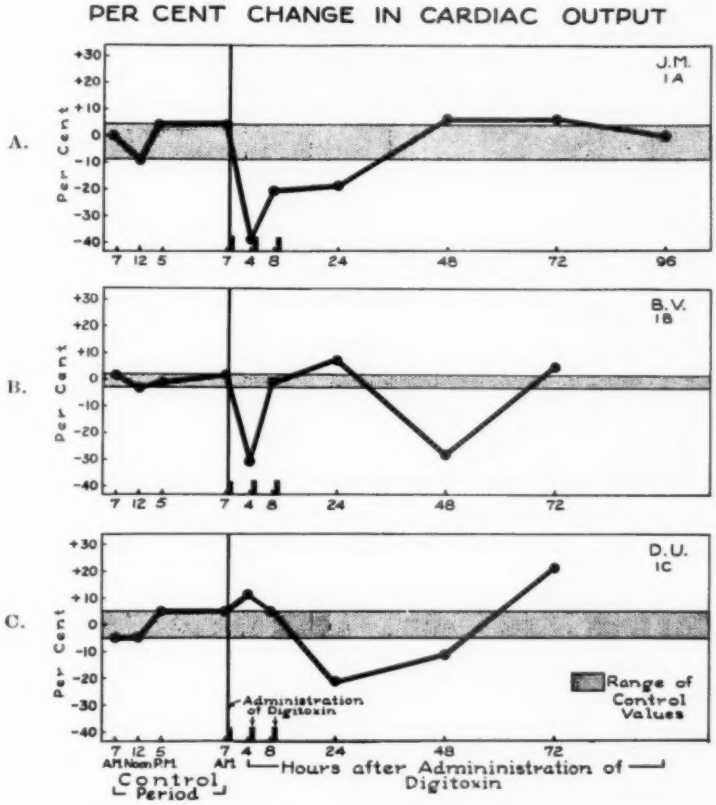

Fig. 1.—The 3 types of changes of minute cardiac output as the result of digitoxin in normal subjects are illustrated. The values after the administration of digitoxin are percentage changes from the mean value observed during the control period. The shaded area represents the maximum deviation occurring during the control period. *A* illustrates the type of response in which there is only an initial fall in minute cardiac output during the first 4 hours (2 subjects). *B* illustrates the type of response in which there is an initial fall in minute cardiac output followed by a temporary rise and then a second fall 24 to 48 hours following administration of the drug (5 subjects). *C* illustrates the third type of response in which there is no fall until the second or third day after the administration of the drug (5 subjects). Note that the falls in cardiac output are well out of the maximum range of deviation which occurred during the control period.

studied. The minute cardiac output had returned to within the control range in all subjects by the sixth day following digitoxin. A decline in cardiac output was considered significant only when the fall was well out of the range of values obtained during a comparable period of control before the administration of digitoxin.

TABLE I. THE APPARENT STROKE VOLUME, MINUTE CARDIAC OUTPUT, BLOOD PRESSURE, AND PERIPHERAL RESISTANCE (DYNES CM.$^{-5}$ SECOND) IN 12 NORMAL SUBJECTS BEFORE AND AFTER THE ADMINISTRATION OF DIGITOXIN

			TIME	STROKE VOLUME (C.C.)	CARDIAC RATE	CARDIAC OUTPUT (L. PER MINUTE)	BLOOD PRESSURE (MM. Hg)	MEAN BLOOD PRESSURE (MM. Hg)	PERIPHERAL RESISTANCE
Subjects with only an initial drop in cardiac output									
J. M.	Before digitoxin		7 A.M.	91	70	6.3	112/86	95	1205
			12 noon	92	63	5.8	114/76	89	1227
			5 P.M.	96	68	6.5	120/76	91	1112
			7 A.M.	82	79	6.5	108/70	83	1014
	Hours after digitoxin	4	12 noon	44	88	3.9	112/72	82	1680
		8	5 P.M.	64	79	5.0	104/68	80	1291
		24	7 A.M.	75	70	5.2	120/74	89	1368
		48	7 A.M.	90	75	6.7	106/68	81	963
		72	7 A.M.	120	56	6.7	110/70	83	987
		96	7 A.M.	97	65	6.3	110/70	83	1053
B. C.	Before digitoxin		7 A.M.	89	78	6.0	112/84	97	1292
			12 noon	79	62	5.0	120/78	92	1471
			5 P.M.	95	68	6.5	120/78	92	1123
			7 A.M.	71	68	4.7	118/80	93	1583
	Hours after digitoxin	4	12 noon	53	63	3.3	122/84	97	2350
		8	5 P.M.	59	63	3.7	124/78	92	1989
		12	7 A.M.	50	65	3.3	110/84	93	2253
		24	7 A.M.	48	71	3.4	120/76	91	2179
		48	7 A.M.	94	61	5.7	118/72	87	1219

Subjects with an initial drop in cardiac output followed by a second fall the second or third day following the administration of digitoxin

B. V.	Before digitoxin		7 A.M.	92	75	6.9	130/86	101	1169
			12 noon	88	74	6.5	130/82	98	1197
			5 P.M.	88	76	6.7	130/80	97	1154
			7 A.M.	99	70	6.9	120/74	89	1031
	Hours after digitoxin	4	12 noon	53	89	4.7	136/80	99	1684
		8	5 P.M.	93	72	6.7	130/76	94	1117
		12	7 A.M.	113	65	7.3	118/72	87	949
		24	7 A.M.	74	65	4.8	132/76	95	1582
		48	7 A.M.	100	72	7.2	132/80	97	1077
M. G.	Before digitoxin		7 A.M.	77	65	5.0			
			12 noon	63	84	5.3			
			5 P.M.	63	68	4.4			
			7 A.M.	74	64	4.7	104/74	84	1429
	Hours after digitoxin	4	12 noon	30	72	2.2	100/60	77	2803
		8	5 P.M.	50	63	3.1	110/60	77	1987
		12	7 A.M.	40	63	2.5	110/60	77	2459
		24	7 A.M.	43	68	2.9	104/76	85	2343
		48	7 A.M.	64	67	4.4	110/74	86	1566
H. W.	Before digitoxin		7 A.M.	72	60	4.3	108/80	89	1654
			12 noon	99	64	6.3	110/82	98	1243
			5 P.M.	94	58	5.4	100/76	87	1287
			7 A.M.	97	63	6.1	110/76	87	1136
	Hours after digitoxin	4	12 noon	43	58	2.5	104/78	87	2778
		8	5 P.M.	60	60	8.6	120/84	96	2131
		12	7 A.M.	76	64	4.9	104/80	89	1386
		24	7 A.M.	65	63	4.0	100/80	87	1890
		48	7 A.M.	89	71	6.3	100/74	83	1053
J. K.	Before digitoxin		7 A.M.	125	56	7.0	122/80	94	1068
			12 noon	152	56	7.5	122/80	94	882
			5 P.M.	149	68	10.3	118/78	91	704
			7 A.M.	135	56	7.6	120/80	94	986
	Hours after digitoxin	4	12 noon	110	58	6.4	116/70	85	1057
		8	5 P.M.	125	56	7.0	132/76	95	1082
		24	7 A.M.	140	58	8.1	122/74	90	888
		48	7 A.M.	80	65	5.8	120/80	93	1293
		72	7 A.M.	74	75	5.5	120/80	93	1354
		96	7 A.M.	111	65	7.2	124/72	89	988

TABLE I—CONT'D

			TIME	STROKE VOLUME (C.C.)	CARDIAC RATE	CARDIAC OUTPUT (L. PER MINUTE)	BLOOD PRESSURE (MM. Hg)	MEAN BLOOD PRESSURE (MM. Hg)	PERIPHERAL RESISTANCE
Subjects with an initial drop in cardiac output followed by a second fall the second or third day following the administration of digitoxin—Cont'd									
J. Br.	Before digitoxin		7 A.M.	113	52	5.9	110/60	73	988
			12 noon	104	65	6.7	110/70	80	952
			5 P.M.	104	59	6.3	110/60	73	926
			7 A.M.	102	65	6.6	104/62	76	912
	Hours after digitoxin	4	12 noon	91	59	5.4	104/62	75	1110
		8	5 P.M.	100	56	5.6	110/64	97	1127
		24	7 A.M.	99	60	5.9	104/60	75	1016
		48	7 A.M.	70	67	4.7	100/64	76	1293
		72	7 A.M.	83	68	5.6	106/60	75	1076
Subjects with an initial rise or no change in cardiac output followed by a drop the second or third day following the administration of digitoxin									
C. C.	Before digitoxin		7 A.M.	64	71	4.5	110/76	87	1724
			12 noon	66	71	4.7	118/76	88	1497
			5 P.M.	97	70	6.0	118/76	92	1065
			7 A.M.	61	75	4.6	120/70	84	1469
	Hours after digitoxin	4	12 noon	89	52	4.6	108/70	83	1443
		8	5 P.M.	103	58	5.9	110/70	83	1127
		24	7 A.M.	96	54	5.2	122/72	89	1369
		48	7 A.M.	65	65	4.3	116/70	85	1579
		72	7 A.M.	80	75	5.6	120/70	87	1242
		96	7 A.M.	107	48	5.1	118/74	89	1394
D. U.	Before digitoxin		7 A.M.	85	65	5.5	116/70	85	1235
			12 noon	83	65	5.4	130/84	99	1466
			5 P.M.	101	60	6.0	122/78	93	1239
			7 A.M.	106	56	6.0	120/70	87	1159

	Hours after digitoxin	4	12 noon	107	60	6.4	124/70	88	1096
		8	5 P.M.	110	54	6.0	128/66	87	1159
		24	7 A.M.	68	65	4.4	130/80	97	1762
		48	7 A.M.	93	54	5.0	120/74	89	1423
		72	7 A.M.	102	68	6.9	122/70	87	1008
T. E.	Before digitoxin		7 A.M.	87	44	3.8	110/86	94	1978
			12 noon	98	47	4.6	112/78	89	1547
			5 P.M.	98	52	5.1	120/80	93	1457
			7 A.M.	99	43	4.3	114/78	91	1672
	Hours after digitoxin	4	12 noon	109	48	5.2	122/66	85	1307
		8	5 P.M.	117	48	5.6	120/68	85	1213
		24	7 A.M.	66	41	2.7	110/74	86	2545
		48	7 A.M.	73	43	3.2	120/80	93	2324
		72	7 A.M.	40	55	2.2	110/70	83	3021
		96	7 A.M.	78	56	4.4	120/80	93	1690
T. L.	Before digitoxin		7 A.M.	71	71	5.1	110/70	83	1301
			12 noon	86	92	7.9	120/78	92	1921
			5 P.M.	66	83	5.5	120/70	87	1276
			7 A.M.	84	70	5.9	110/72	85	1152
	Hours after digitoxin	4	12 noon	90	80	7.2	120/70	87	965
		8	5 P.M.	72	78	5.6	120/68	85	1214
		24	7 A.M.	71	65	4.6	110/68	82	1426
		48	7 A.M.	42	79	3.3	114/70	85	2058
		72	7 A.M.	74	78	5.8	116/64	81	1117
J. B.	Before digitoxin		7 A.M.	77	65	5.0	104/80	88	1407
			12 noon	77	63	4.7	118/88	98	1667
			5 P.M.	61	65	4.0	106/70	82	1680
			7 A.M.	70	68	4.7	110/78	89	1565
	Hours after digitoxin	4	12 noon	65	61	3.9	120/84	96	1967
		8	5 P.M.	59	60	3.5	120/80	93	1970
		24	7 A.M.	43	70	3.0	124/84	97	2584
		48	7 A.M.	69	68	4.7	120/80	93	1582

TABLE II. CHANGES FROM THE MEAN IN THE POSTEROANTERIOR DIASTOLIC AND SYSTOLIC CARDIAC DIAMETERS FOLLOWING THE ADMINISTRATION OF DIGITOXIN IN 12 NORMAL SUBJECTS (THE APPARENT STROKE VOLUME IS INSERTED FOR THE VARIOUS PERIODS.)

	CONTROL PERIOD				HOURS AFTER THE ADMINISTRATION OF DIGITOXIN											
	DIASTOLIC DIAMETER MAXIMUM†		SYSTOLIC DIAMETER MAXIMUM†		4 STROKE VOLUME		8 STROKE VOLUME		24 STROKE VOLUME		48 STROKE VOLUME		72 STROKE VOLUME		96 STROKE VOLUME	
	MEAN*	VARIATIONS	MEAN*	VARIATIONS	DIASTOLIC‡	SYSTOLIC‡	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC
J. M.	7.77	+0.58 −0.34	7.26	+0.61 −0.35	44 −0.06	+0.21	64 +0.38	+0.53	75 +0.06	+0.20	90 −0.18	−0.17	120 −1.19	−1.48	97 +0.26	+0.25
B. C.	7.07	+0.38 −0.27	6.56	+0.51 −0.32	53 +0.16	+0.34	59 +0.18	+0.44	50 −0.22	−0.08	48 −0.32	−0.11	94 −0.09	−0.16		
B. V.	7.40	+0.15 −0.05	6.87	+0.61 −0.38	53 +0.72	+1.00	93 +0.64	+0.68	113 +0.64	+0.58	74 +0.54	+0.68	100 +0.32	+0.30		
M. G.	6.99	+0.11 −0.20	6.56	+0.09 −0.04	30 +0.51	+0.74	50 +0.01	+0.23	40 −0.07	+0.12	43 −0.07	+0.10	64 −0.16	−0.13		
H. W.	6.29	+0.13 −0.13	5.67	+0.12 −0.15	43 +0.60	+0.96	60 −0.59	−0.42	76 −0.61	−0.59	65 −0.02	+0.16	89 +0.08	+0.10		
J. K.	7.47	+0.75 −0.34	6.66	+0.78 −0.40	110 +2.23	+2.52	125 −0.19	−0.12	140 −0.91	−1.04	80 −1.34	−1.16	74 −0.09		111 −1.49	−1.50
J. Br.	7.18	+0.35 −0.45	6.53	+0.41 −0.53	91 +0.40	+0.54	100 +0.40	+0.49	99 −0.24	−0.20	70 +0.40	+0.66	83 +1.73	+1.94		
C. C.	6.78	+0.04 −0.04	6.31	+0.13 −0.10	89 +0.10	+0.02	103 +0.32	−0.17	96 +0.10	−0.03	65 −0.04	+0.02	80 −0.24	−0.29	107 +0.40	+0.23
J. B.	7.25	+0.23 −0.14	6.83	+0.31 −0.18	65 −0.27	−0.24	59 −0.14	−0.07	43 −0.27	−0.11	69 −0.05	+0.07				
D. U.	6.40	+0.90 −0.72	5.74	+1.00 −0.89	107 −1.27	−0.61	110 −1.64	−0.98	68 −1.47	−0.81	93 −1.75	−1.09	102 −1.37	−0.54		
T. L.	7.12	+0.17 −0.11	6.66	+0.13 −0.27	90 +0.47	+0.43	72 +0.47	+0.54	71 +0.31	+0.27	42 −0.39	−0.19	74 −0.15	−0.14		
T. E.	6.69	+0.64 −0.52	6.07	+0.69 −0.64	109 +1.08	+1.10	117 −0.07	−0.06	66 −0.23	−0.04	73 −0.36	−0.24	40 −0.40	−0.11	78 −0.36	−0.27

*The mean value listed is the average of the 7 A.M., 12 noon, 5 P.M. values on the control day and the 7 A.M. value on the morning before the administration of digitoxin.

†The variations listed are the maximum and minimum variations from the mean during the same control period.

‡Variations in centimeters of the diastolic and systolic posteroanterior diameters from that of the mean during the control period.

The minute cardiac output decreased an average maximum of 37 per cent in the 12 subjects studied as the result of digitoxin.

There were very few symptoms noted in the subjects following digitalis. However, when they did occur, they usually paralleled the fall in cardiac output. The symptoms were lethargy, weakness, fatigue, slight nausea, transient anorexia, and drowsiness. One subject had no symptoms associated with an appreciable fall in minute cardiac output (M. G.).

Even with the administration of a total of 2 mg. of digitoxin, only slight changes were noted on the electrocardiograms, characterized by diminished height of the T waves.

The Effect of Digitoxin on the Pulse Rate, Blood Pressure, and Peripheral Resistance.—Only 1 of the 12 subjects demonstrated any significant slowing of the cardiac rate. (In this 1 subject the heart rate decreased from a control value of 70 beats per minute to 48 beats per minute on the fourth day after the administration of digitoxin.) There was no appreciable effect on the mean blood pressure; however, there was a tendency for the pulse pressure to widen. The average of all the pulse pressures during the control period was 38 mm. Hg as compared to 43 mm. Hg 4 hours after the administration of digitoxin, 48 mm. Hg after 8 hours, and 42 mm. Hg after 24 hours. Peripheral resistance was elevated during the period when the minute cardiac output was decreased (see Table I).

The Effect of Digitoxin on the Posteroanterior Cardiac Diameters.—Table II includes the changes in the posteroanterior cardiac diameters (diastolic and systolic) during the periods of observation following the administration of digitoxin as they varied from the mean diameters during the control period before the administration of digitoxin. The apparent stroke volumes are inserted. Although only the posteroanterior diameters were measured, it is probable that changes in volume were reflected in these measurements, since the position of the subject was the same in all observations. There is no reason to believe that the heart could increase or decrease in volume without a comparable increase or decrease in the posteroanterior diameters, provided the position of the subject remains constant.

It is noted (Table II) that the posteroanterior cardiac diameters did not decrease 4 hours after the administration of digitoxin even in the presence of a lower cardiac output in the 7 subjects who had an initial fall in minute cardiac output. In all but 1 subject (J. B.) there occurred, usually 8 to 12 hours after the administration of digitoxin, a decrease in the posteroanterior diastolic diameter, associated with no change or an increase in the apparent stroke volume. In each such instance, there was a greater proportional decrease in the systolic posteroanterior diameter than in the diastolic diameter. A decreasing posteroanterior cardiac diameter in the presence of a rise in stroke volume or without a fall in stroke volume suggests that the heart is emptying more completely during ejection.

The time when the maximum decrease in diameters occurred was variable; however, in most subjects they decreased 24 to 48 hours after the administration

of digitoxin. During this period the second or delayed fall in cardiac output usually occurred as noted in 10 of the 12 subjects. The decrease in diameters usually lasted only 2 days. It is considered that the decrease in posteroanterior diastolic size was significant. Table III lists the mean value for the 2 7 A.M. control periods and the 2 maximum decreases noted following the administration of digitalis. In analyzing the data, it was necessary to select values from each subject at different times, since the decrease in the diameters did not occur uniformly on the same day. In order to overcome the objection of selecting values following the administration of digitoxin, not only was the greatest decrease in diameters in each subject compared to the 7 A.M. control values, but the 2 smallest diameters from each subject following the administration of digitoxin were compared to the 7 A.M. control values. The calculations were based upon the variations from the control values determining the probable error of the differences. The chances were 3.09 out of 100 that the maximum decrease in diameters was due to chance occurrence only. The chances were 6.87 out of 100 that the 2 smallest diameters following the administration of digitoxin from each subject, as compared to the 7 A.M. control values, were due to chance occurrence only.

TABLE III. THE MEAN OF THE 2 7 A.M. CONTROL POSTEROANTERIOR CARDIAC DIAMETERS IS LISTED AS WELL AS THE 2 SMALLEST DIAMETERS WHICH OCCURRED FOLLOWING THE ADMINISTRATION OF DIGITOXIN, IRRESPECTIVE OF THE TIME IN WHICH THEY OCCURRED

SUBJECTS	AVERAGE OF THE 2 7 A.M. CONTROL VALUES (CM.)		SMALLEST POSTEROANTERIOR DIAMETER FOLLOWING ADMINISTRATION OF DIGITOXIN (CM.)		THE NEXT SMALLEST POSTEROANTERIOR DIAMETER FOLLOWING ADMINISTRATION OF DIGITOXIN (CM.)	
	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC
J. M.	7.59	7.11	6.58	5.78	7.59	7.09
B. C.	7.13	6.65	6.75	6.45	6.85	6.48
B. V.	7.45	6.91	7.72	7.17	7.94	7.55
M. G.	7.10	6.65	6.83	6.43	6.92	6.66
H. W.	6.18	5.59	5.66	5.08	5.70	5.25
J. K.	7.04	6.23	5.98	5.16	6.13	5.50
J. Br.	7.11	6.43	6.94	6.33	7.58	7.19
C. C.	6.78	6.39	6.54	6.02	6.74	6.33
J. B.	7.13	6.35	6.98	6.76	7.11	6.72
T. L.	7.02	6.55	6.73	6.47	6.97	6.52
D. U.	6.49	5.85	5.41	4.65	5.47	4.93
T. E.	6.63	6.03	6.23	5.96	6.33	5.83
Mean	6.97	6.40	6.36	6.02	6.77	6.34

In comparing the 2 7 A.M. control periods to the maximum decrease noted in Column 3 in the diastolic diameters following the administration of digitoxin, the chances were 3.09 out of 100 that a decrease in magnitude of that degree could occur by chance only.

In comparing the 2 7 A.M. control periods to the 2 smallest diastolic diameters (Columns 3 and 5) in each subject following the administration of digitoxin (irrespective of the time in which they occurred), the chances were 6.86 out of 100 that an over-all decrease of that degree could occur by chance only.

In all instances, as the diastolic posteroanterior diameter diminished, the systolic diameter diminished also. The excursion produced by the systolic contraction (difference between the diastolic and systolic posteroanterior diameters) decreased in all subjects as the stroke volume fell.

The Effect of Digitoxin on the Phases of the Cardiac Cycle.—Control border tracings of the left ventricle and aortic knob were recorded before the digitoxin was given. In all subjects this was done on the morning of the administration of digitoxin. In 4 subjects, 3 separate control tracings were recorded at 7 A.M., 12 noon on the control day, and 7 A.M. on the morning before the administration of digitoxin to be sure that the duration of the phases did not change appreciably from observation to observation and from day to day. No significant change was noted until the digitoxin was ingested.

TABLE IV. THE EFFECT OF DIGITOXIN ON THE DURATION IN SECONDS OF THE RAPID EJECTION PHASE OF THE CARDIAC CYCLE IN 12 NORMAL SUBJECTS

SUBJECT	BEFORE DIGITOXIN				HOURS AFTER ADMINISTRATION OF DIGITOXIN					
					4	8	24	48	72	96
	7 A.M.	12 NOON	5 P.M.	7 A.M.	12 NOON	5 P.M.	7 A.M.	7 A.M.	7 A.M.	7 A.M.
J. M.				0.14		0.10	0.11	0.14	0.15	0.20
B. C.				0.12	0.10	0.11	0.09	0.11	0.17	
B. V.				0.16		0.13	0.14		0.19	
M. G.				0.17		0.12		0.13		
H. W.	0.19	0.18	0.20	0.19	0.16	0.14	0.15	0.17	0.19	
J. K.	0.20	0.18		0.20	0.17	0.16	0.15	0.17	0.16	0.18
J. Br.	0.19	0.16		0.20	0.12	0.12	0.14	0.16	0.13	
C. C.				0.20	0.17	0.18	0.16	0.18	0.22	
J. B.				0.15		0.16				
T. L.				0.18		0.15	0.15		0.15	
D. U.	0.18	0.15		0.17	0.18	0.17	0.18	0.16	0.18	
T. E.				0.23	0.19	0.14	0.20	0.20	0.15	0.18
Mean	0.19	0.17		0.18	0.16	0.14	0.15	0.15	0.16	0.19

The duration of total systole in 12 subjects before the administration of digitoxin averaged 0.32 second (4 observations on each subject) with an average heart rate of 65 beats per minute as compared to 0.29 second after the administration of digitoxin (6 observations on each subject), again with an average heart rate of 65 beats per minute. The shortening of total systole was chiefly due to the decrease in duration of the rapid ejection phase. It is noted in Table IV that the maximum decrease in duration of the rapid ejection phase occurred 12 to 24 hours after ingestion of digitoxin, which was also the time the posteroanterior cardiac diameters were beginning to decrease. The duration of rapid ejection tended to return to control values by the fifth day following the initial administration of digitoxin (Table IV). As previously pointed out, the duration of reduced ejection is related to changes in rate.[17] No consistent change in this phase was noted following the administration of digitoxin. Isometric contraction was not significantly affected.

The most remarkable effect of digitoxin on the phases of diastole was the lengthening of the rapid filling phase. This phase became prolonged 4 hours following the administration of digitoxin and was still prolonged, although somewhat less, the fifth day. Table V records the duration in seconds for the phase of rapid filling.

TABLE V. THE EFFECT OF DIGITOXIN ON THE DURATION IN SECONDS OF THE RAPID FILLING PHASE OF THE CARDIAC CYCLE IN 12 NORMAL SUBJECTS

SUBJECT	BEFORE DIGITOXIN				HOURS AFTER ADMINISTRATION OF DIGITOXIN					
					4	8	24	48	72	96
	7 A.M.	12 NOON	5 P.M.	7 A.M.	12 NOON	5 P.M.	7 A.M.	7 A.M.	7 A.M.	7 A.M.
J. M.				0.17		0.24	0.20	0.22	0.24	0.21
B. C.				0.20	0.32	0.32	0.36	0.24	0.18	
B. V.				0.14		0.20	0.24		0.20	
M. G.				0.18		0.26		0.24		
H. W.	0.15	0.17	0.17	0.15	0.25	0.21	0.25	0.19	0.19	
J. K.	0.16	0.12		0.16	0.24	0.26	0.26	0.23	0.28	0.26
J. Br.	0.14	0.20		0.14	0.23	0.25	0.25	0.26	0.20	
C. C.				0.20		0.21	0.26	0.32	0.28	0.24
J. B.				0.24		0.26				
T. L.				0.17		0.18	0.24		0.24	
D. U.	0.16	0.18		0.14	0.21	0.24	0.26	0.24	0.17	
T. E.				0.14	0.28	0.24	0.30	0.22	0.24	0.22
Mean	0.15	0.17		0.17	0.25	0.24	0.25	0.24	0.21	0.23

There was a tendency for the duration of rapid filling to be longest during periods when the apparent stroke volume was the lowest in the individual subjects; however, the mean values for the various periods did not demonstrate this correlation. Fig. 2 is a composite representation of the mean values of the apparent stroke volume, duration of rapid filling, rapid ejection, and postero-anterior cardiac diameter during the various periods following the administration of digitoxin. Diastasis became shorter in duration as rapid filling lengthened. As previously mentioned, there was no appreciable difference in heart rate before and after digitoxin. The duration of isometric relaxation plus protodiastole did not change from the control following the administration of digitoxin (Table VI). The importance of this will be discussed subsequently.

Records of the right ventricular border and pulmonary artery were taken in 5 subjects. The changes noted from the right ventricle and pulmonary artery were similar to those found on the left side of the heart, varying only slightly in magnitude. Fig. 3 illustrates the parallelism of the duration of the rapid filling phase as measured from right and left ventricles at various periods following the administration of digitoxin in 1 subject.

The Effect of Digitoxin on the Contour of the Electrokymographic Border Tracings.—Following the administration of digitoxin to normal subjects, the pattern of the left ventricular tracings was markedly altered. In contrast to the

control tracing, which was characterized by a rapid ascent during filling followed by a plateau in diastasis, the ventricular tracings after the administration of digitoxin assumed a slow ascending curve throughout diastole. This was primarily due to a slower rate of ventricular diastolic filling, as indicated by the prolonged rapid filling phase. Fig. 4, *A* and *B*, is an example of the ventricular border tracing before and after the administration of digitoxin. The upward

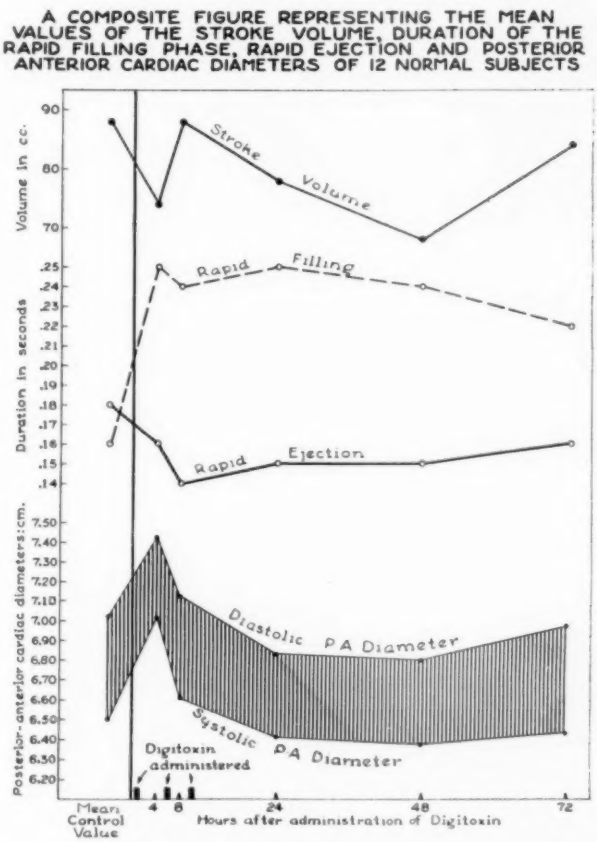

Fig. 2.—The mean values from the 12 normal subjects for the apparent stroke volume, duration of the rapid filling phase, duration of rapid ejection, and the posteroanterior diastolic and systolic diameters are recorded for the various periods of observation following the administration of digitoxin. Note that the first fall in stroke volume, 4 hours after the administration of digitoxin, was associated with a slight increase in the posteroanterior cardiac diameters, suggesting incomplete systolic emptying. The fall in the stroke volume was probably the result of a combination of a transient increase in peripheral resistance and diminished venous return to the heart, as indicated by a prolonged duration of the rapid filling phase. About 8 hours after the administration of digitoxin, the cardiac diameters decreased, associated with a rise in stroke volume, indicating a more complete systolic emptying during ejection. The duration of rapid ejection decreased, adding further evidence that there was an increase in the strength of contraction at that time. Twenty-four to 48 hours after the administration of digitoxin, the posteroanterior cardiac diameters decreased, associated with the second fall in stroke volume. The duration of the rapid filling phase is an indication of the rate of ventricular diastolic filling.[19] The prolongation noted indicates that the heart fills slower as the result of digitoxin throughout the entire period. The presence of a slow rate of ventricular diastolic filling, diminished heart volume, and a low stroke volume, as occurs 24 to 48 hours after the administration of digitoxin, indicates that the minute volume of blood returning to the heart is diminished possibly as the result of a peripheral effect of digitoxin. As the stroke volume rose 72 hours after the administration of digitoxin, the heart size was returning toward control values as was the duration of the rapid filling phase and rapid ejection.

small spike just following the onset of ventricular contraction, which has been attributed to positional movements,[16] often became very peaked and increased in height following the administration of digitoxin (Fig. 4,*C*). It is quite possible that the peak noted early during systole was the cause for the apparent increase in excursion of systolic contraction noted by Cohn and Stewart[3] in dogs following the administration of digitalis. As already pointed out, there was actually a decrease in the size of the excursion as the result of systolic contraction following the administration of digitoxin.

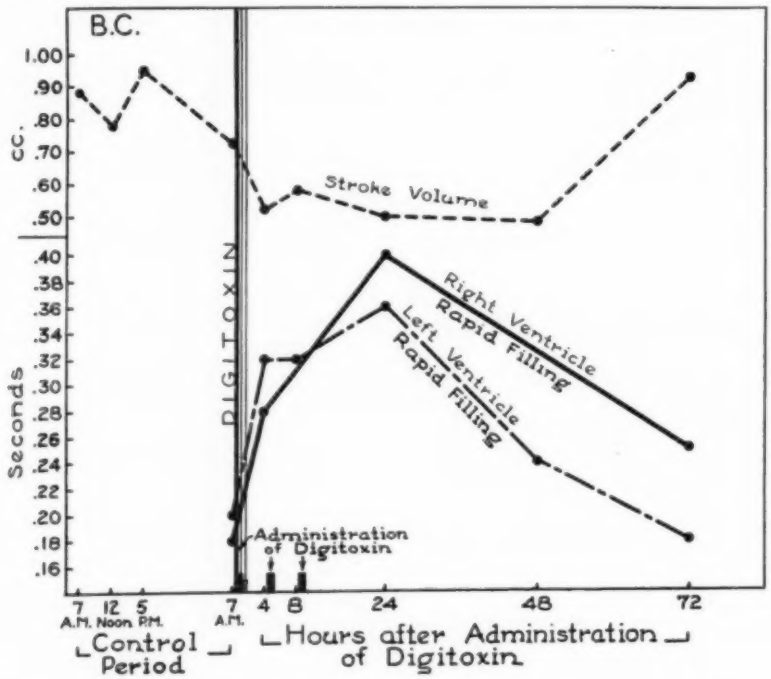

Fig. 3.—The relation of the duration of the rapid filling phase of the left and right ventricles is illustrated. The duration of the rapid filling phase as measured from both left and right ventricular border tracings is plotted for the various periods before and after the administration of digitoxin. The apparent stroke volume is also included. It is noted that both sides have a similar lengthening of rapid filling indicating a slower rate of ventricular diastolic filling. Because of the parallelism between the 2 sides of the heart, it is probable that there is no selective action of digitoxin on the pulmonary circulation in normal subjects.

The tracings obtained from the aortic knob after digitoxin were characterized by a more rapid upsweep during ejection, as compared to the control tracing. This was associated with a decrease in the duration of the rapid ejection phase.

DISCUSSION

The Phase of Decreased or Normal Cardiac Output With No Change in Heart Size.—Apparently the response of normal subjects to the oral administration of digitoxin is variable during the first 4 to 8 hours. Five of the 12 subjects studied did not have a fall in minute cardiac output during this initial period. Those subjects in whom there was a fall in cardiac output 4 hours after the initial administration of digitoxin had no significant change in the posteroanterior

cardiac diameters at that time. There are 3 possible explanations for the combination of events noted in these latter subjects: (1) decrease in the strength of myocardial contraction, (2) incomplete systolic emptying as the result of an increased load under which the heart works (peripheral resistance), and (3) the combination of a diminished minute volume of venous return and incomplete systolic emptying.

TABLE VI. THE EFFECT OF DIGITOXIN ON THE DURATION IN SECONDS OF THE ISOMETRIC RELEXATION PHASE PLUS PROTODIASTOLE IN 12 NORMAL SUBJECTS (ONLY THE MEAN VALUE IS LISTED FOR THE DIFFERENT PERIODS OF OBSERVATION.)*

	BEFORE DIGITOXIN				HOURS AFTER ADMINISTRATION OF DIGITOXIN					
					4	8	24	48	72	96
TIME	7 A.M.	12 NOON	5 P.M.	7 A.M.	12 NOON	5 P.M.	7 A.M.	7 A.M.	7 A.M.	7 A.M.
Mean	0.15	0.14		0.13	0.14	0.13	0.14	0.15	0.15	

*Protodiastole remained constant (0.04 second); thus, by subtracting this value from the above mean the value of isometric relaxation could be obtained.

In considering the first postulation, it is unlikely that digitalis could act first as a poison and then a stimulant. As will be pointed out, it is probable that the strength of contraction is increased 8 to 24 hours after the administration of digitoxin. If digitalis actually depressed the myocardial strength, adverse clinical effects should be observed following digitalization of patients in congestive failure.

In connection with the second possibility (decreased emptying), there is evidence that the peripheral load on the heart may be at least temporarily increased in some subjects. The peripheral resistance was increased in those subjects who exhibited a decrease in the cardiac output 4 hours after the administration of digitoxin (Table I). However, it is uncertain from our data whether or not the increased peripheral resistance resulted in the fall in cardiac output or that the increased peripheral resistance was a reflex phenomenon as the result of a diminished cardiac output. Unquestionable elevations in blood pressure have been noted after toxic doses of digitalis.[22] However, with therapeutic doses, the effect on blood pressure is transient when such effects occur.[23] The fact that changes in blood pressure occurring after the administration of therapeutic doses of digitalis have been so seldom noted indicates that this is an inconstant effect of digitalis. In summary, the evidence obtained from the present study and from the work of other investigators indicates that although digitalis may exert an effect on blood pressure and peripheral resistance, the effect is not profound. It seems unlikely, therefore, that the initial fall in cardiac output in 7 of the 12 subjects could be solely the result of an increase in the load under which the heart worked.

It is more likely that the third possibility (a combination of diminished venous return and an increase load on the heart) occurred. The duration of the rapid filling phase, as previously pointed out,[19] is an indication of the rate of ven-

tricular diastolic filling.[19] The duration of this phase becomes prolonged when the subject is standing, after venesection, and with the application of venous tourniquets about the thighs.[13] A rise in ventricular diastolic pressure or a decrease in atrial pressure would be expected to prolong the rate of ventricular diastolic filling or to lengthen the duration of the rapid filling phase of the cardiac cycle. From Table V it can be seen that this phase was unquestionably prolonged

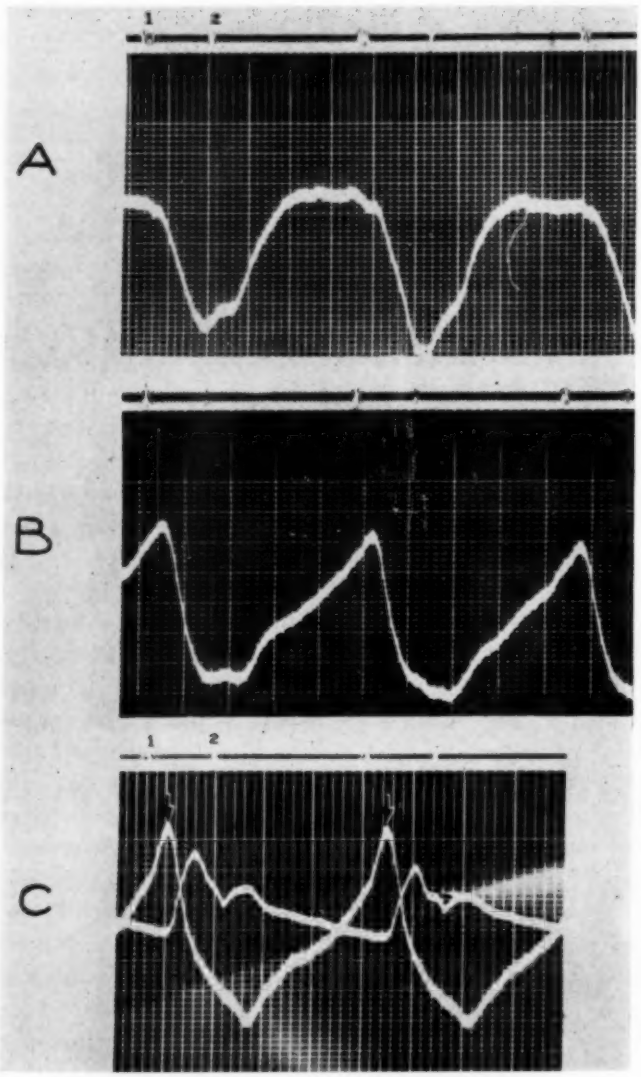

Fig. 4.—The effect of digitoxin on the contour of the left ventricular border tracings is illustrated. *A* illustrates the type of tracing occurring before the administration of the drug in 1 subject. Note the plateau type of curve, indicating a rapid filling of the ventricle, followed by a period of diastasis before the onset of ventricular contraction. *B* illustrates the effect of digitalis on the left ventricular border tracing in the same subject. Note the relatively slow diastolic filling with apparently some filling occurring during the entire diastolic period. *C* illustrates the enlarged upward peak (as indicated by the arrow) during isometric contraction as the result of digitoxin. The peak is probably the result of increased positional movements of the heart.

as the result of digitoxin, indicating a slower rate of ventricular diastolic filling. Although a rise in intraventricular diastolic pressure cannot be excluded, it is unlikely that it occurs, as will be pointed out. Thus, it is likely that the minute volume of blood returning to the heart was decreased as the result of digitoxin. (This will be discussed in more detail later.) A small, but otherwise insignificant, increase in the peripheral load on the heart could result in a definite fall in output in the presence of a diminishing venous return. Thus, the fall in cardiac output noted 4 hours after the administration of digitoxin was probably the result of the inconstant increase in peripheral resistance and the diminishing venous return to the heart. In the subjects in whom no fall in cardiac output occurred, it is probable that the peripheral load on the heart was minimal and that the minute volume of blood returning to the heart had not yet diminished sufficiently to decrease the output.

The Phase of Decreasing Heart Size With No Change or Rise in Cardiac Output.—Eight to 24 hours after the initial dose of digitoxin, there was noted a decrease in the posteroanterior cardiac diameters, associated with either no change or a rise in the apparent stroke volume (Table II, Fig. 2). A decreasing heart size associated with an increase or lack of change in stroke volume indicated that at this time there was an increase in the strength of contraction and more complete systolic emptying. In most instances the stroke volume actually increased, resulting in the type of response in cardiac output noted in Fig. 1,*B*.

The duration of the rapid ejection phase is probably an index of the strength of contraction.[19] The duration of the rapid ejection phase usually decreased to the greatest degree at the time the heart size was beginning to diminish, thus adding further evidence to the hypothesis that the strength of the contraction was increasing at this point (Table IV, Fig. 2). The aortic ejection tracings taken at this time also exhibited a more rapid upsweep than those of the control tracings. These findings of increased strength of contraction after digitalis confirmed the cardiotonic effect noted on isolated cardiac muscle strips,[13] as well as in the dog's heart,[22] as the result of this drug. From this evidence, therefore, it is likely that digitalis does increase the strength of contraction at a given fiber length, probably reaching the maximum effect 8 to 24 hours after the oral administration of digitoxin.

The Phase of Decreased Heart Size With Decreased Cardiac Output.—Twenty-four to 36 hours after the initial dose of digitoxin, there was again noted a fall in minute cardiac output. This fall occurred during the period of the maximum decrease in the posteroanterior cardiac diameters. In some of the subjects this was the time when the heart was filling the slowest, as indicated by the prolongation of the rapid filling phase (Table V). Rytand has shown that the venous pressure exhibits a maximal fall at approximately this same time after the administration of digitalis.[24]

This diminution in heart size which has been described by others has been attributed by them to the presence of increased cardiac tone. A decrease in size of the heart could, however, indicate that there was less venous return to the heart per unit of time and need not be attributed to an increase in the "tone." "Tone" of the heart muscle has been described as a resistance of the heart to

diastolic filling or a state of partial contraction of the heart muscle.[25] Meek has pointed out that to demonstrate an increase in "tone" it would be necessary to find changes in diastolic relaxation.[25] Both of these factors of a partial state of contraction or resistance to diastolic relaxation would lengthen the time for the intraventricular pressure to fall below that of the atrium following systolic contraction. Thus, if increased "tone" occurred following the administration of digitoxin, there would be expected an increase in the duration of the isometric relaxation phase of the cardiac cycle (time for the intraventricular pressure to fall below that of the atrium which opens the valves between the atrium and the ventricle, allowing filling to begin). As noted from Table VI, the duration of isometric relaxation was not altered following the administration of digitoxin. Gold and Cattell also were unable to demonstrate any increase in "tone" of a papillary muscle from the cat's heart as the result of digitalis.[13] Thus, a slower rate of ventricular diastolic filling without an increase in the resistance of the myocardium to relax under the filling pressure (without prolongation of the isometric relaxation phase) indicates that the rate of blood returning to the ventricles has been altered.

Theoretically, an increase in the ventricular diastolic pressure could reduce the atrioventricular pressure gradient and thus prolong the rapid filling phase. Such a decrease in the atrioventricular pressure gradient is extremely improbable, however, since it has been demonstrated that digitalis causes a fall in the right atrial pressure.[12] A rise in ventricular diastolic pressure and a fall in auricular pressure is physiologically unlikely since the diastolic pressure changes in the 2 cavities generally parallel each other. Therefore, the decrease in atrial[12] and venous pressures[24] following the administration of digitalis, previously noted by other investigators, indicates that the atrioventricular pressure gradient is diminished by a peripheral rather than a central effect. If the decrease in pressure noted was only the result of a more efficient emptying of the ventricles, a greater differential pressure between the atrium and ventricular pressure would result, and, consequently, a shorter duration for the rapid filling phase of the cardiac cycle would be expected. This shortening was not observed in these subjects after digitalization. It is probable that a decrease in blood volume return to the heart, indicated by the slower rate of rapid filling, was responsible for the decrease in minute cardiac output noted on the third day after the administration of digitoxin. About this time, the diastolic posteroanterior cardiac diameter, and probably the heart volume, was the smallest (Fig. 2) and was associated with a slower rate of ventricular diastolic filling, indicating a diminished volume of blood returning to the heart. Thus, the decrease in cardiac size, noted both in the present study and in the work of other investigators in both man[26] and dogs,[3,4] is apparently due in large part to a diminished minute volume of blood returning to the heart, as well as to the occurrence of more complete systolic emptying.

HYPOTHESES FOR THE MECHANISM OF ACTION OF DIGITALIS

From the data presented above, it appears probable that digitalis exerts the following effects on the cardiovascular system: (1) It increases the strength

of contraction of the heart, producing more complete systolic emptying; (2) it diminishes the minute volume of venous return to the heart, possibly as the result of venous constriction; and (3) it increases the peripheral resistance, probably due to an effect on the arteriolar bed. This last change appears transient and slight. In addition to these effects, it is remotely possible that the large arteries are constricted, resulting in the widening of the pulse pressure as noted in this study of normal subjects. In other words, digitalis exerts a stimulating effect of variable degree on all the muscular elements of the vascular system, both central and peripheral.

The fall in the cardiac output during the first 4 hours following the administration of digitoxin is probably the result of the transient peripheral effect of arteriolar constriction and the diminishing venous inflow to the heart as the result of venous constriction. About 8 hours after the oral administration of digitoxin, the strength of contraction of the heart is significantly increased, resulting in a rise in the minute cardiac output (Fig. 2). With a constantly diminishing venous return, however, the cardiac output cannot be maintained even in the face of more complete systolic emptying. This accounts for the late fall in cardiac output occurring 24 to 48 hours after the oral administration of digitoxin (Fig. 2). It is also probable that the effective circulating blood volume has diminished at this point. It has been shown in previous studies that digitalis reduces the blood volume both in the human subjects and in the experimental animal.[27,28] In another study on the blood volume in dogs following the intravenous administration of digitalis,[29] the plasma volume was estimated to decrease 8 to 33 per cent, associated with an expansion of the thiocyanate space. Since venous constriction alone produces a similar reduction in the effective circulating blood volume,[30] it seems highly probable that such constriction is operative following the administration of digitalis. The blood volume apparently is reduced fairly rapidly following venous constriction, a part of the decrease being due to increase in capillary filtration with a passage of fluid into the extracellular space and a part due to a pooling of blood in unknown stores.[30] It is likely that the effective circulating blood volume is the significant factor in determining the level of the cardiac output.

Reference to the literature reveals that little investigation has been concerned with the direct effect of digitalis on the veins. Gottlieb and Mangus have shown in the dog that strophanthin in large doses results in constriction of the vessels of the kidney, intestine, and spleen.[31] This constrictor effect has been confirmed by Impens.[32] Although the blood flow in the legs was found to be increased after strophanthin, if the splanchnic area was eliminated by evisceration, then this drug was found to act as a constrictor on the vessels of the leg of the dog.[31] However, in these studies no differentiation was made between the arteries and the veins, since the constrictor effect was determined by observing that strophanthin reduced the blood flow from the veins draining the area in question. Digitalin in dilutions of 1:50,000 was found by Franklin to constrict isolated segments of the jugular and mesenteric veins of the sheep and to constrict the mesenteric vein of the cat.[33] Cushny stated that constriction unquestionably occurred with poisonous doses of digitalis; however, with smaller

doses the effect was found to be less marked.[22] Thus, from the pharmacological evidence there is a constrictor effect on veins and other vessels as well, the magnitude and importance of which seem variable with therapeutic doses of digitalis.

SUMMARY AND CONCLUSIONS

The effect of oral digitoxin on the apparent stroke volume, cardiac output, and phases of the cardiac cycle was studied with the electrokymograph in 12 normal subjects. The determinations were followed over a period of a week. The following findings were noted:

1. Three types of cardiac output responses were noted in these normal subjects. The first type of response was characterized by an initial fall in the minute cardiac output, occurring during the first 4 hours (2 subjects). A second group of 5 subjects revealed an initial fall in minute cardiac output which quickly returned to normal, followed by a second drop 24 to 36 hours after the administration of digitoxin. The third group had a fall in cardiac output only after a period of 24 to 36 hours following the administration of digitoxin (5 subjects).

2. The initial fall in cardiac output noted in 7 of the subjects (4 hours after the initial administration of digitoxin) was possibly the result of a transient increase in the load on the heart, due to peripheral vasoconstriction, associated with a simultaneous diminution in venous return to the heart.

3. The strength of contraction of the myocardium increased as the result of digitoxin, as indicated by a more rapid upsweep of the ejection curve and a decrease in duration of the rapid ejection phase. Further evidence indicating increased strength of myocardial contraction was noted in the decrease in postero-anterior cardiac diameter, associated with a simultaneous rise in the stroke volume.

4. Following the administration of digitoxin, there was a slower rate of ventricular diastolic filling as indicated by a lengthening of the duration of the rapid filling phase. This lengthening of the rapid filling phase probably indicates a diminished volume of venous return to the heart.

5. The duration of the phases of the cardiac cycle, as determined from the right and left ventricles, was not significantly different. From these findings, digitoxin did not appear to exert a special effect on the pulmonary circulation.

From the above evidence it appears probable that digitoxin acts both to decrease the volume of blood returned to the heart and to increase the force of cardiac contraction. The major fall in minute cardiac output in normal subjects is attributed to the predominance of the factor of diminished venous return.

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ATRIAL FLUTTER

II. Methods of Treatment

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THE management of atrial flutter has given rise to considerable controversy. Even though the mechanism has been considered by some to be the same as that of atrial tachycardia, its response to therapy is definitely different. There appears to be a general agreement that the circurhythmia should be abolished, preferably by reversion to sinus rhythm, but if that is not possible, by reversion to atrial fibrillation. Although digitalis decreases the ventricular rate in atrial flutter by increasing the degree of atrioventricular block, exercise in digitalized patients with persisting flutter may temporarily decrease the grade of block and thus produce periods of rapid ventricular action. Atrial fibrillation is generally considered preferable to atrial flutter because the ventricular rate in atrial fibrillation is easier to control.

There is no unanimity of opinion regarding the treatment of choice in atrial flutter. Most schemes for reversion employ digitalis preparations or quinidine, singly, in sequence, or in combination. It is probable that the optimum schedule varies with the clinical condition of the patient and the duration of the disorder.

The classical method of management of atrial flutter was first proposed by Lewis[1] (see Table I) and consisted of the administration of digitalis until atrial fibrillation was produced. The digitalis was then discontinued in the hope that the digitalis-induced fibrillation would revert to normal rhythm. However, this program worked satisfactorily in only 3 of the 8 cases in the series of Lewis. A year later, Ritchie[2] noted that the plan was successful in only about one-half of the cases and suggested that digitalis adequate to control the ventricular rate might be preferable.

The management may fail at each point of the desired sequence of events. Following adequate digitalization, the arrhythmia may persist. Other patients may remain in atrial fibrillation permanently after conversion from atrial flutter. Rarely patients may be transformed apparently directly to sinus rhythm. However, in some of the cases quoted where there has been direct conversion, the temporary state of atrial fibrillation may well have been missed. Institution of quinidine therapy[3] has been occasionally successful in restoring sinus rhythm if fibrillation persists after digitalis has been withdrawn.

Parkinson and Bedford[4] (see Table I) in an extensive study of 52 cases of atrial flutter were able to restore normal rhythm through conversion to atrial

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Supported in part by a grant-in-aid from the H. H. Weinert Fund for Cardiovascular Research.

Presented at the Regional Meeting of the American College of Physicians, Jan. 13, 1951, at Memphis, Tenn.

Received for publication Sept. 1, 1950.

fibrillation in 9 of 20 cases with digitalis alone and in 6 of 16 additional cases in which quinidine was also used. In one-fourth of their patients, the disorder persisted despite digitalis administration. These investigators found that oral quinidine in doses to 30 to 40 gr. daily produced sinus rhythm in only 3 of 15 of their patients. In 6 additional patients in whom atrial fibrillation had been induced by digitalis, quinidine restored normal rhythm in 3 and caused return to flutter in 3.

TABLE I. PERCENTAGE EFFICACY OF VARIOUS METHODS IN RE-ESTABLISHING SINUS RHYTHM

	DIGITALIS LEAF	DIGITALIS GLYCOSIDES	DIGITALIS AND QUINIDINE IN SEQUENCE	QUINIDINE ALONE	DIGITALIS AND QUINIDINE CONCURRENTLY
Lewis[1] (8 patients)	8 cases, 38%				
Parkinson and Bedford[4] (52 patients)	20 cases, 45%	Strophanthin I.V., 4 cases, 75%	Digitalis before or after quinidine, 16 cases, 38%	15 cases, 20%	
Bell and Strong[5] (52 patients)	Includes glycosides; 25 cases, 40%	Cedilanid I.V., 4 cases, 50%		13 cases, 69%	8 cases, 25%
Fahr and LaDue[15] (7 patients)		Cedilanid, 7 cases, 71%			
Sokolow and Chamberlain[16] (17 patients)		Cedilanid, 17 cases, 82% (14 cases directly)			
Tandowsky and associates[17] (20 patients)		Cedilanid, 20 cases, 20% (direct conversion)	Cedilanid, then quinidine, 15 cases, 86%		
Herrmann and Hejtmancik (82 patients)	25 cases, 48%	Cedilanid I.V., 4 cases, 25%; digoxin I.V., 2 cases, 50%; digitoxin P.O., 6 cases, 50%	Digitalis leaf, then quinidine, 4 cases, 100%	28 cases, 64%	10 cases, 40%

Bell and Strong[5] (see Table I) in a series of 52 cases of atrial flutter were able to restore sinus rhythm in 12 of 29 patients to whom digitalis preparations were given. In 4 of these patients Cedilanid was given intravenously, and sinus rhythm resulted in 2. Reversion to sinus rhythm was accomplished in 9 of 13 patients given quinidine, but the need for frequent, heavy doses was stressed. Combination of quinidine and digitalis resulted in restoration of sinus rhythm in only 2 of the 8 patients treated.

Other investigators have epitomized their experiences in using digitalis preparations without quoting actual case reports. Sodeman and Engelhardt[6] estimated that when atrial fibrillation is established, 60 per cent of the patients

revert to normal rhythm after digitalis is discontinued. Bellet[7] concluded that digitalis will break up atrial flutter in about 70 per cent of the cases, and that two-thirds of the patients in whom atrial fibrillation is established revert to normal rhythm after digitalis is discontinued. He further stated that one-half of the remainder were then converted to sinus rhythm with quinidine.

The sequence of conversion of atrial flutter to sinus rhythm by way of atrial fibrillation with digitalis is not supported according to the discussion of the literature by Bloomfield[8] and his reported experiences. He decried the classic interruption of digitalis therapy to permit the intervention of normal mechanism and did not definitely recognize any tendency of the digitalis to perpetuate the fibrillation. He has advised the primary use of quinidine if prompt restoration of normal rhythm is desired.

Quinidine without digitalis has been stated to be successful in as high as 65 per cent of the patients with atrial flutter and fibrillation,[9,10] but the supporting clinical case data for atrial flutter are not recorded. Gold[11] suggested the use of quinidine in suitable cases before any other drug because of its rapid elimination in case of failure or idiosyncrasy.

THE PRESENT STUDY

In a recent analysis of atrial flutter[12] occurring 93 times in 82 patients, it seemed desirable to determine the indications and effectiveness of the various therapeutic methods used to terminate the disorder. The patients were seen and treated at the University of Texas School of Medicine in the past 22 years. The cases were divided into transient and established flutter, depending upon whether the duration of the disorder was less or greater than an arbitrarily chosen period of 72 hours. Since the different methods used in various cases were generally well documented, an opportunity was offered for comparison of their efficacy.

EFFECTS OF THERAPY

Transient Flutter.—In Table II are summarized the results of therapy in 28 episodes of atrial flutter of less than 72 hours' duration before reversion. Digitalis (powdered leaf) changed 1 directly to sinus rhythm and changed the other 4 to atrial fibrillation. Three of these 4 patients reverted to sinus rhythm after digitalis was discontinued, but in 1 of these quinidine was added before reversion. After digitalis was withheld, the fourth patient again showed atrial flutter. Oral digitoxin instituted sinus rhythm directly in 1 patient and failed to influence the flutter in another. Intravenous digoxin re-established sinus rhythm apparently directly in 1 case. Cedilanid, 1.6 mg., given intravenously, converted the atrial flutter to atrial fibrillation in 1 case but failed to change the arrhythmia in another.

Quinidine sulfate by mouth was very effective in this group and instituted sinus rhythm in all 7 cases in which it was given. The total dosage of oral quinidine in the previous 24 hours before reversion in this group varied from 0.6 to 2.2 Gm., with an average of 1.44 Gm.

TABLE II. TREATMENT OF TRANSIENT ATRIAL FLUTTER

	CASES	FAILED	TO SINUS DIRECTLY	TO ATRIAL FIBRILLATION	ATRIAL FIBRILLATION TO SINUS WHEN DIGITALIS WAS DISCONTINUED
Digitalis (Powdered leaf)	5	0	1	4	3*
Digitoxin (1.2 mg. oral)	2	1	1		
Cedilanid (1.6 mg. I.V.)	2	1		1	
Digoxin (1.5 mg. I.V.)	1		1		
Quinidine (orally)	7		7		
Digitalis and quinidine concurrently	2	2			
No treatment	9	1	8		

*Quinidine added before reversion in 1 patient.

In 8 of 9 cases atrial flutter changed spontaneously to sinus rhythm within 72 hours of its onset. A total of 6 patients died with atrial flutter of less than 72 hours' duration. Two were in uremia, and 1 had disseminated carcinoma. Two patients had acute myocardial infarcts. The final patient was in congestive failure despite full digitalization. The oral administration of 1.3 Gm. of quinidine sulfate to this patient had no effect on the arrhythmia.

Persistent Flutter.—The results of therapy of 55 episodes in 48 patients with flutter persisting over 72 hours are summarized in Table III. Spontaneous disappearance of atrial flutter while under observation was rare in this group. In the 24 patients to whom digitalis leaf was administered, 5 were refractory, 5 changed to sinus rhythm without a recorded period of atrial fibrillation, and 14 were converted to atrial fibrillation. When the digitalis was withheld in 10 of the patients with digitalis-induced atrial fibrillation, 4 changed to sinus rhythm; 3 more changed when quinidine therapy was begun. Two patients changed back to atrial flutter, and the remaining patient remained in persistent atrial fibrillation. The intravenous glycosides were less successful in our experience, but the patients to whom they were given were usually in more serious condition. The dosages of the intravenous glycosides were in amounts usually regarded as adequate for full digitalization, but they were not pushed beyond these values.

Oral quinidine was less effective in persistent flutter than in the short-duration group, but it terminated the disorder by direct conversion to sinus rhythm in 10 of 19 cases. The amount of quinidine sulfate used in the successful cases in the 24 hours before reversion varied from 0.8 to 3.2 Gm., with an average of

1.74 Gm. However, all 9 in whom quinidine had failed were subsequently converted to sinus rhythm or atrial fibrillation. In these, cessation of quinidine and use of digitalis converted 3 to sinus rhythm, 3 to atrial fibrillation and thence to sinus rhythm upon withdrawal of digitalis, and 3 to permanent atrial fibrillation.

TABLE III. TREATMENT OF ESTABLISHED ATRIAL FLUTTER

	TRIALS	FAILED	TO SINUS DIRECTLY	TO ATRIAL FIBRILLATION	ATRIAL FIBRILLATION TO SINUS WHEN DIGITALIS WAS DISCONTINUED
Digitalis (Powdered leaf)	24	5	5	14	7*
Digitoxin (1.2 mg. oral)	4	1	2	1	
Cedilanid (1.6 mg. I.V.)	2	1	1		
Digoxin (1.5 mg. I.V.)	1	1			
Quinidine (orally)	19	9	10		
Quinidine (I.V.)	2	1	1		
Digitalis and quinidine concurrently	8	4	4		
Procaine (I.V.)	2	2			

*Digitalis was discontinued in 10 patients; oral quinidine was added in 3.

Concurrent digitalis and quinidine resulted in establishing sinus rhythm in 4 of 8 cases.

In 8 of the patients with persistent flutter the disorder continued until discharge or death. In 2, death was due to malignancy, and in 2 death resulted from myocardial infarction with complicating atrial flutter. Four patients with refractory atrial flutter were discharged fully digitalized with slow ventricular rates. Two of these later reverted apparently spontaneously to normal rhythm.

The efficacy of the various therapeutic methods in re-establishing sinus rhythm in the entire series of both transient and persistent flutter is summarized and compared to other reports in Table I.

Flutter With Myocardial Infarction.—In 12 patients of this series atrial flutter occurred as a complication of acute myocardial infarction. This is a serious complication of myocardial infarction, and Askey[13] observed that 12 of 19 such patients died during hospitalization, 8 with the atrial flutter unchanged. Five of our 12 patients died with persisting atrial flutter, and 1 additional patient died during hospitalization despite reversion to sinus rhythm with oral quinidine. One of the patients had 1:1 conduction and died before any specific treatment was given. Another had atrial flutter with complete atrioventricular block. Digi-

talis changed the disorder to atrial fibrillation, in 2 patients. Quinidine restored sinus rhythm in 3 patients, the drug being given orally to 2 and intravenously to 1. Two patients reverted spontaneously to normal rhythm.

Flutter With 1:1 Conduction.—Atrial flutter with 1:1 atrioventricular conduction presents a cardiac emergency because of the rapid ventricular rate. It was recorded in 5 of our patients. One with myocardial infarction died before any specific therapy could be given. Another, also with myocardial infarction, was restored to sinus rhythm with 2.0 Gm. of oral quinidine sulfate in divided doses, but soon died. One patient with uremia was converted to atrial fibrillation with Cedilanid, 1.6 mg. given intravenously, but died of a renal disorder. Another patient with congenital heart disease and congestive failure had the disorder following an episode of paroxysmal atrial tachycardia and died on the same day, still with atrial flutter, despite 1.3 Gm. of oral quinidine sulfate. The final patient, a 32-year-old white man with no apparent organic heart disease, had an episode of 1:1 atrial flutter and syncope following oral quinidine sulfate given to institute sinus rhythm in flutter with 2:1 atrioventricular block. He was promptly digitalized to increase the degree of block to 2:1 and to produce atrial fibrillation. This reverted to sinus rhythm after the digitalis was withheld.

DISCUSSION

The tabulated results in our own and other series demonstrate well the efficacy of digitalis leaf in terminating atrial flutter, usually by way of atrial fibrillation. Digitalis leaf converted atrial flutter to atrial fibrillation in 18 of our cases and converted directly to sinus rhythm in an additional 6 of the 29 cases of atrial flutter in which it was used. In the 14 cases of atrial fibrillation in which digitalis was then discontinued, 10 changed to sinus rhythm, but 4 of these also received quinidine soon after digitalis was withdrawn.

There are theoretical and practical advantages in using certain purified glycosides which are more rapidly metabolized and dissipated than the powdered leaf. Digitalization can be accomplished more quickly with crystalline pure glucosides, and any toxic effects that may occur are more evanescent. It would appear that a more prompt conversion to sinus rhythm, either directly or through atrial fibrillation, may thus be attained. Digitoxin, however, is slowly eliminated and does not possess these advantages. Schaaf and co-workers[14] demonstrated these properties in the treatment of 2 patients with digoxin. Reports by Fahr and LaDue[15] and Sokolow and Chamberlain[16] (see Table I) have shown conspicuous effectiveness of intravenous Cedilanid in the direct conversion of atrial flutter to sinus rhythm. However, Tandowsky and associates[17] noted this direct establishment of sinus rhythm by Cedilanid in only 4 of 21 cases of established atrial flutter, a much lower percentage. Since most of their patients were converted to sinus rhythm through a period of atrial fibrillation, they advocated a combination of Cedilanid and quinidine sulfate in sequence to convert successfully atrial flutter to sinus rhythm.

Our experiences have not confirmed an increased efficacy of the quicker-acting digitalis glycosides. There were 3 failures in 6 cases in which intravenous glycosides were used, but these failures were no doubt partly due to the more

critical condition of our patients. Digitoxin given orally as 1.2 mg. converted 3 patients apparently directly to sinus rhythm and 1 to atrial fibrillation and was unsuccessful in the remaining 2. Intravenous compounds have been effective in individual cases, and further studies with these drugs are desirable. Even if the arrhythmia is unchanged, the prompt increase in atrioventricular block by rapid digitalization provides marked relief in atrial flutter in the patients with rapid ventricular rates and probably protects against the serious development of a 1:1 mechanism.

Digitalization is the procedure of choice in atrial flutter whenever there is cardiac decompensation or severe organic heart disease and usually in long-standing cases. Even in the occasional refractory case, it provides a suitably slow ventricular rate by increasing the atrioventricular block. When atrial fibrillation is produced, withdrawal of digitalis frequently results in the institution of sinus rhythm, particularly if oral quinidine is then begun. Flutter occasionally reappears, and in these cases we have stopped quinidine if the flutter persists for several days despite adequate dosage. However, Goldman[18] noted a frequent occurrence of atrial flutter in quinidine therapy of atrial fibrillation, and from his cases concluded that if the dosage of quinidine in such circumstances was maintained or increased, regular sinus rhythm would usually result.

Quinidine has been used in the treatment of atrial flutter since its value was demonstrated by Wenckebach[19] in 1914. Recent studies[20,21,22] using the photofluorometric method of Brodie and Udenfriend[23] to determine plasma quinidine levels have confirmed the rapid absorption of oral quinidine found by Weisman.[24] The plasma quinidine levels were found by Kalmansohn and Sampson[20] to be maximal in ½ to 4¼ hours, but still 42 to 73 per cent of the maximum persisted for 8 hours, and as high as 22 per cent for 24 hours. A cumulative effect was present for 72 hours, as demonstrated by a rising blood level for this period on constant dosage by Sokolow and Edgar,[22] after which there was a parabolic fall. These observers found 75 per cent of a series of 30 patients with atrial flutter and fibrillation to revert to sinus rhythm on plasma levels of 4 to 9 mg. per liter. This was obtained with quinidine doses of 0.4 to 0.9 Gm. orally every 2 hours for 5 doses. If these amounts were not successful, higher dosages and higher plasma levels were relatively ineffective. The actual concentration of quinidine in the myocardium apparently follows the plasma levels. However, it may be of more significance than plasma concentrations, as demonstrated by conversions of circurhythmias after the peak plasma concentrations have been passed and by several conversions in our experience 12 to 24 hours after oral quinidine was discontinued.

Quinidine in our series was usually administered to patients not presenting serious heart disease, not in decompensation, and not presenting any contraindication to its use, as toxicity or idiosyncrasy. Adequate amounts are to be stressed, and usually doses of 0.2 to 0.3 Gm. were given each hour following a test dose of 0.1 Gm. The atrial flutter rate usually slows as the tissue concentrations of quinidine increase and, as a result, may decrease to 200 or 175 per minute. At this relatively slow atrial rate there may occur 1:1 conduction, which may result in syncope and collapse. The rapid ventricular rate in such cases may be

of grave consequence in a seriously diseased heart, and if untoward symptoms appear, rapid intravenous digitalization is indicated in the emergency thus created.

Oral quinidine sulfate given alone in this series was successful in 17 of the total number of 26 patients to whom it was given. There was a direct conversion to sinoatrial rhythm in all successful instances. Quinidine was particularly effective in atrial flutter of short duration. Some of these results may have been coincidental.

One patient was converted to sinoatrial rhythm with intravenous quinidine. This was given as quinidine lactate, 0.6 Gm. in 200 c.c. of 5 per cent glucose, administered as a slow drip (15 to 30 drops per minute) under continuous electrocardiographic control. This is indicated in all instances in which intravenous quinidine is given to record the onset and progression of intraventricular conduction defects and to anticipate more serious mechanism disturbances. Frequent blood pressure determinations must be taken during the drip to warn of serious hypotensive reactions, particularly in hypertensive patients. We[25] have considered QRS prolongation of over 25 per cent as an indication to discontinue treatment. This was the reason for stopping the medication in another patient with atrial flutter to whom intravenous quinidine was given without changing the circurhythmia.

In the 9 instances of quinidine failure, all of duration over 72 hours, the atrial flutter in each was promptly and effectively managed by later digitalization. The probability of such prompt conversion in event of failure of quinidine appears to be one of the advantages of giving quinidine first in suitable cases.

Quinidine administered alone should be used to institute sinus rhythm in atrial flutter only in the absence of contraindications, which include idiosyncrasy to quinidine or toxic effects, congestive heart failure, embolic phenomena, and syncopal attacks during cinchonization. The depressant myocardial effects of quinidine would usually contraindicate its use in congestive heart failure until after the circulation had been compensated with digitalis. Serious organic heart disease, particularly if associated with chronic atrial flutter, would usually contraindicate the use of quinidine. This is especially true if bundle branch block is present.[26] The occasional sudden increase in ventricular rate due to quinidine producing a 1:1 conduction may impose a serious burden on the failing heart.

Other Methods Used in Atrial Flutter.—No other therapeutic methods have been conspicuous in permanently influencing atrial flutter. Carotid sinus stimulation resulted in a temporary increase in the atrioventricular block in about two-thirds of our patients with atrial flutter, most often in those with already increased vagal tone due to previous digitalization. However, the increase in atrioventricular block was only transient, as no cases of atrial flutter were terminated by carotid sinus stimulation alone. This is in marked contrast to the efficacy of carotid sinus stimulation in converting one-half of our cases with paroxysmal atrial tachycardia to normal sinus rhythm.

Although Prostigmine and Mecholyl are frequently effective in paroxysmal atrial tachycardia, both of these preparations failed in several of our cases of atrial flutter in which they were tried. Mecholyl has been reported to terminate an attack of atrial flutter,[27] but such results are unusual and side effects are frequent.

Intravenous procaine has proved of little value and failed in 2 of our patients to whom total doses of 250 mg. were given. Fagarine was recommended as of value in terminating atrial flutter by Taquini.[28] However, Scherf and associates[29] have observed 2 instances of fatal ventricular fibrillation with the use of fagarine, and thus it would appear too dangerous to use in this condition. Atrial flutter in 1 case has been reported as terminated by Atabrine.[30]

Prevention of Recurrences.—After reversion to sinus rhythm, maintenance therapy aimed at reduction of atrial irritability appears desirable, at least for a short period of time. This is especially true of the recurrent paroxysmal types where it should be continued indefinitely. Maintenance therapy in our cases usually consisted of small oral doses of quinidine sulfate, 0.2 Gm., 3 to 4 times daily. Several recurrences occurred on this maintenance regime, but usually in patients who were also being given digitalis or in patients who discontinued the maintenance therapy. Daily oral doses of Cedilanid were advised by Tandowsky and co-workers[17] to prevent recurrences. Occasionally, small doses of potassium, such as saturated solution of potassium iodide, and a diet high in potassium have proved helpful. Hungarian paprika, which contains a high percentage of potassium, may be used at each meal to increase the potassium intake.

SUMMARY

1. Results of therapy are summarized in 28 episodes of transient (less than 72 hours' duration) atrial flutter in 24 patients and in 55 episodes of established (more than 72 hours' duration) atrial flutter in 48 patients.

2. Digitalis is the drug of choice in the management of atrial flutter in patients with serious organic heart disease or cardiac decompensation, or where there is a specific contraindication to quinidine. It usually acts by instituting atrial fibrillation, which reverts to sinus rhythm on its withdrawal, particularly if quinidine is then given. Even in the refractory cases, or when permanent atrial fibrillation is established, the slow ventricular rate maintained by digitalis provides for adequate cardiac function. Digitalis may also convert the atrial flutter directly to sinus rhythm, but in some of these cases a temporary period of atrial fibrillation may be missed.

3. With the exception of increased rapidity of digitalization, the pure crystalline oral and intravenous digitalis glycosides showed little advantage over digitalis leaf in this series. However, these preparations were outstanding in certain individual cases and deserve further study.

4. Oral quinidine sulfate alone proved effective in restoring sinus rhythm in selected patients without cardiac decompensation and without grave organic heart disease, particularly if the atrial flutter was of short duration. It has the disadvantage of being a myocardial depressant and on rare occasions initiates 1:1 conduction with the hazards of a rapid ventricular rate.

5. In unusually refractory cases, when previous attempts have been unsuccessful in influencing the circurhythmia, intravenous quinidine lactate or gluconate may be justified in the attempt to institute sinoatrial rhythm, but only with frequent blood pressure determinations and under constant, direct electrocardiographic control.

6. Combinations of quinidine and digitalis concurrently were less effective than either alone or in sequence, but they appear desirable whenever atrial flutter

occurs in acute myocardial infarction with cardiac decompensation, and when 1:1 rhythm has once developed with quinidine alone.

7. Maintenance doses of quinidine, potassium, or possibly Cedilanid are variously dependable after reversion in preventing recurrences.

8. Prognosis, in general, depends upon the underlying myocardial condition. It is particularly poor whenever atrial flutter complicates myocardial infarction and when atrial flutter is an episode in terminal states.

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EFFECTS OF EXERCISE ON CIRCULATORY DYNAMICS IN MITRAL STENOSIS. III.

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THE symptoms of mitral stenosis are attributable mainly to congestive phenomena in the lungs, and these, in turn, are due to the pulmonary circulatory changes consequent to the narrowed mitral valve. Although circulatory abnormalities are usually present even at rest, these abnormalities become magnified under conditions of increased bodily work. Meakins and associates[1] first pointed out the limited circulatory response to exercise in these patients. This observation has subsequently been confirmed in recent studies[2,3] by the technique of cardiac catheterization.

METHODS

Eight patients who had stenosis of the mitral valve predominantly and minimal degrees of other valvular involvement were studied a total of nine times by the technique of cardiac catheterization. The clinical diagnoses, functional classification,[4] physiologic data, and the calculated mitral valve area[5] for each of these patients are seen in Table I. The patients were rehearsed by exercising them on the bicycle ergometer in the laboratory the day before the actual procedure and were instructed in the use of the mouthpiece for expired air collection. On the day of study, they fasted or else received a light breakfast of orange juice, toast, jam, and black coffee. No sedative was administered. Cardiac catheterization was performed in the usual fashion. Pulmonary "capillary" pressure[6] was recorded at rest (after five minutes or more, during which time pulse and respiration had become stable) and again during exercise (at the second minute of a three-minute period of exercise, as described later). Sufficient time was allowed between exercise periods to allow pulse and respiration to return to normal, usually ten minutes or more.

The catheter was then withdrawn to a point just distal to the bifurcation of the pulmonary artery. A No. 20 or 21 short-bevel needle was inserted into the brachial artery, the lumen of which was kept patent by a slow intravenous

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This work was supported in part by grants from the National Heart Institute, United States Public Health Service, and the Life Insurance Medical Research Fund.

Received for publication Oct. 13, 1950.

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Table I. Physiologic Data in Patients With Mitral Stenosis at Rest and During Exercise

TABLE I. PHYSIOLOGIC DATA IN PATIENTS WITH MITRAL STENOSIS AT REST AND DURING EXERCISE

PATIENT	CLINICAL CLASSIFICATION	MITRAL VALVE AREA ($CM.^2$)	RHYTHM	STATE	ARTERIAL OXYGEN SATURATION (%)	OXYGEN CONSUMPTION (C.C. PER MINUTE)	A-V OXYGEN DIFFERENCE (C.C. PER LITER)	CARDIAC OUTPUT (LITER PER MINUTE)	CARDIAC INDEX (LITER PER MINUTE PER SQ. M.)	PULSE RATE (PER MINUTE)	STROKE INDEX (C.C. PER BEAT PER SQ. M.)	A-P DIAMETER OF CHEST (CM.)	MEAN PRESSURES (MM. HG)				RESISTANCES (DYNES SECOND CM.-5)		WORK OF VENTRICLE AGAINST PRESSURE (KG. M. PER MINUTE PER SQ. M.)	
													PULMONARY ARTERY	PULMONARY "CAPILLARY"	BRACHIAL ARTERY	RIGHT AURICLE	PULMONARY ARTERIOLAR	TOTAL PERIPHERAL	RIGHT VENTRICLE	LEFT VENTRICLE
J. D.	I	2.5	SR	R	100	281	30	9.4	5.2	100	52	18	25	19	91	9	51	775	1.2	6.4
				E	100	803	72	11.1	6.1	120	51		47	41			43		3.3	
J. F.	II	1.6	SR	R	99	254	39	6.5	3.8	72	54	22	32	21	92	9	135	1130	1.3	4 8
				E	99	656	70	9.4	5.5	108	51		58	46			102		3.9	
L. T.	III	0.9	SR	R	99	262	59	4.4	2.5	70	35	18	45	24	71	5	382	1290	1.4	2.4
				E	97	609	109	5.7	3.2	108	30		82	46	84	10	504	1175	3.3	3.6
M. B.	IV	0.8	AF	R	94*	194	61	3.2	2.0	96	20	18	23	17		14	150		0.26	
				E		379	79	4.8	2.9	93	32		36	28			133		0.92	
E. S.	IV	0.7	AF	R	97	216	55	3.9	2.4	80	31	19	48	26	96	4	451	1970	1.5	3.1
				E	97	369	91	4.1	2.6	94	27		68	51			332		2.4	
E. S.	IV	0.7	AF	R	97	190	58	3.3	2.1	84	24	19	38	28		6	242		0.96	
				E	97	348	85	4.1	2.6	70	37		52	35		7	332		1.7	
N. L.	IV	0.6	SR	R	85	272	86	3.2	1.9	105	18	19	66	28	83	14	950	2080	1.4	2.1
				E	90	528	131	4.0	2.4	136	18		83	35	80		960	1600	2.4	2.6
R. W.	IV	0.6	SR	R	99	163	46	3.5	2.6	70	38	18	46	34	69	9	274	1580	1.4	2.4
				E	99	240	60	4.0	3.0	120	29		65	47	47	11	360	940	2.3	1.8
M. M.	IV	0.4	AF	R	99	154	66	2.3	1.4	56	25		55	22	108	10	1150	3760	0.90	2.1
				E	95	227	80	2.8	1.7	136	13		79	35	95	21	1260	2710	1.4	2.2
Average				R	97	221	56	4.4	2.7	81	33		42	24	83†	8†	421	2178†	1.2	2.3†
				E	97	462	86	5.6	3.3	110	32		65	40	77	12	447	1606	2.4	2.6

R = Rest
E = Exercise
*Sample obtained immediately after procedure.
†Average computed using only those studies where observations were made both at rest and during exercise.

saline solution infusion. After pulse and respiration had returned to the initial resting level, a resting cardiac output was measured by the direct Fick method. Expired air was collected for three minutes in a Douglas bag, and blood samples were withdrawn simultaneously from the brachial artery and pulmonary artery midway during the gas collection. Immediately thereafter, pressures in the pulmonary and brachial arteries were recorded. Pressures were then taken after two minutes of exercise. Expired air was collected between 2.5 and 3.0 minutes. Midway during the collection of the expired air, blood samples were withdrawn from the pulmonary and systemic arteries simultaneously. The volume of expired air was measured in a Tissot spirometer, and the concentration of oxygen alone was measured by a Pauling oxygen analyzer. From previous studies[7] of Haldane analysis of expired air, mean correction factors of 1.007 and 1.01, respectively, were derived for converting expired volume to inspired volume under resting conditions and during exercise. The volume of oxygen inspired was therefore calculated as per cent inspired oxygen times volume of expired air times 1.007 or 1.01. Blood samples were analyzed for oxygen content, capacity, and saturation by the method of Van Slyke and Neill[8] and the arteriovenous oxygen difference calculated. In one-half of the patients, the catheter was then withdrawn to the right auricle where pressures were obtained at rest and after two minutes of exercise.

Pressures were measured with Hamilton manometers[9] or, in the latter part of the series, with electromanometers*[10] which recorded on a multi-channel, direct-writing oscillograph. The recording was calibrated with a mercury manometer after each pressure tracing. The zero point for all pressures was 10 cm. anterior to the back with the patient recumbent. A saline manometer was used for checking mean pressures but not for analytical purposes. Mean pressures were obtained by planimetric integration of the pressure tracings when the Hamilton manometer was used, and by electrical integration when the oscillographic tracings were used. The mean pressure gradient between pulmonary artery and pulmonary "capillaries" (PA-"PC") was obtained by subtraction.

The area of the mitral valve orifice was calculated as described elsewhere[5] by the following formula:

$$MVA = \frac{MVF}{31\sqrt{\text{"PC"} - 5}}$$

where MVA = mitral valve area, cm.^{2}

MVF = mitral valve flow, c.c. per second $\left(\frac{\text{cardiac output, c.c. per minute}}{\text{diastolic filling period, seconds per minute}}\right)$

"PC" = pulmonary "capillary" pressure, mm. Hg

5 = assumed left ventricular mean diastolic pressure, mm. Hg

31 = empirical constant.

*Sanborn Company, Cambridge, Mass.

The resistances were calculated according to the Poiseuille equation, where $\text{Resistance} = \frac{\text{Pressure gradient}}{\text{Rate of blood flow}}$. Pulmonary arteriolar resistance was calculated as follows:

$$R = \frac{PA_m - \text{“}PC_m\text{”}}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

The total peripheral resistance was calculated as follows[11]:

$$R' = \frac{BA_m - O}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

where PA_m = pulmonary artery mean pressure, mm. Hg
$\text{“}PC_m\text{”}$ = pulmonary “capillary” mean pressure, mm. Hg
BA_m = brachial artery mean pressure, mm. Hg
CO = cardiac output, c.c. per second
1,332 = conversion factor from mm. Hg to dynes per cm.^{2}

Ventricular work against pressure was calculated as follows[11]:

$$W_R = \frac{(CI \times 1.055)\ ([PA_m - RA_m] \times 13.6)}{1000} \text{ kg.M. per minute per sq.M.}$$

$$W_L = \frac{(CI \times 1.055)\ ([BA_m - 5] \times 13.6)}{1000} \text{ kg.M. per minute per sq.M.}$$

where W_R = work of right ventricle against pressure
W_L = work of left ventricle against pressure
CI = cardiac index, liters per minute per sq.M.
1.055 = specific gravity of blood
PA_m = pulmonary arterial mean pressure, mm. Hg
RA_m = right atrial mean pressure, mm. Hg
BA_m = brachial arterial mean pressure, mm. Hg
5 = assumed left ventricular diastolic pressure, mm. Hg
13.6 = specific gravity of mercury.

Exercise was performed with the patient recumbent, pedalling a bicycle at the rate of 56 r.p.m., timed with a metronome. All but one patient pedalled the bicycle for a three-minute period. Patient M. M. performed only one minute of exercise, during which time the various studies were performed. The pedal resistance was varied from patient to patient, and no attempt was made to express external work performed. Because of variations in efficiency among patients, the oxygen consumption was used as an index of work performed. In order to observe direction of change with exercise, all values were plotted against oxygen consumption per square meter.

Data in the patients before and after each exercise period[7] are seen in Table II. Recovery pulses and pressures in the pulmonary artery and pulmonary

"capillaries" were taken for comparison to resting values in six of the nine studies. It will be observed that except for patient N. L., the values had returned to pre-exercise levels by the two- or the five-minute observation. It may be shown by the use of hydraulic formulas described elsewhere[5] that when pulmonary "capillary" pressure and pulse were similar before and after exercise, cardiac output must have been similar also. Studies of other circulatory diseases[12,13] have indicated similar resting and recovery values. Because of this consistent reproducibility of values, it was felt that data obtained during different periods of standard exercise would be superimposable for purposes of comparison in the resting and exercise state.

TABLE II. COMPARISON OF PULMONARY DYNAMICS BEFORE AND ON RECOVERY FROM EXERCISE IN MITRAL STENOSIS

PATIENT	PULMONARY "CAPILLARY" PRESSURE (MM. HG)		PULMONARY ARTERY MEAN PRESSURE (MM. HG)		PULSE RATE (PER MINUTE)	
	BEFORE	TWO MINUTES AFTER	BEFORE	TWO MINUTES AFTER	BEFORE	TWO MINUTES AFTER
J. D.	19	20	25	33	100	92
J. F.	21	20	32	34	72	73
N. L.	28	33	66	93	105	125
R. W.			46	53	70	76
M. M.*	22	25	55	56	56	56
L. T.*	24	26	45	53	70	76

*Recovery values obtained five minutes after cessation of exercise.

OBSERVATIONS

With exercise, oxygen consumption increased 1.5 to 3 times the resting value of 120 to 160 c.c. per square meter of body surface. As was expected, the rise in consumption was least in those with the least exercise tolerance and the most severe disease (see Table I). Arterial oxygen saturation was normal at rest and during exercise in eight studies and went from 85 to 90 per cent in one patient (N. L.) who also had severe pulmonary vascular disease, as judged by calculated arteriolar resistance. Cardiac output per square meter of body surface rose significantly in one patient (J. F.), whose resting blood flow was normal, and somewhat in two (M. B. and L. T.), who had a low cardiac output at rest (Fig. 1). In five of the other six studies, resting cardiac outputs were low. No significant change took place with exercise. Conversely, in these five, arteriovenous oxygen differences rose sharply beyond normal limits with exercise (Fig. 1). With a fixed cardiac output, the rise of oxygen consumption was directly proportional to the extraction of oxygen from blood by the tissues.

Although resting pulses showed a wide scatter at rest, only in three individuals did pulses rise during exercise above the upper limit of normal for the patients studied in this laboratory (Fig. 1). One patient with auricular fibrillation (E. S.) actually had a fall in pulse rate on exercise.

Patients J. D. and J. F. with mild mitral stenosis (see Table I) had normal stroke outputs at rest and upon exercise (Fig. 1). The remaining seven had low-normal or low stroke outputs at rest; only two of them (E. S. and M. B.) showed an increase on exercise. In neither of these two did pulse rate increase with exercise.

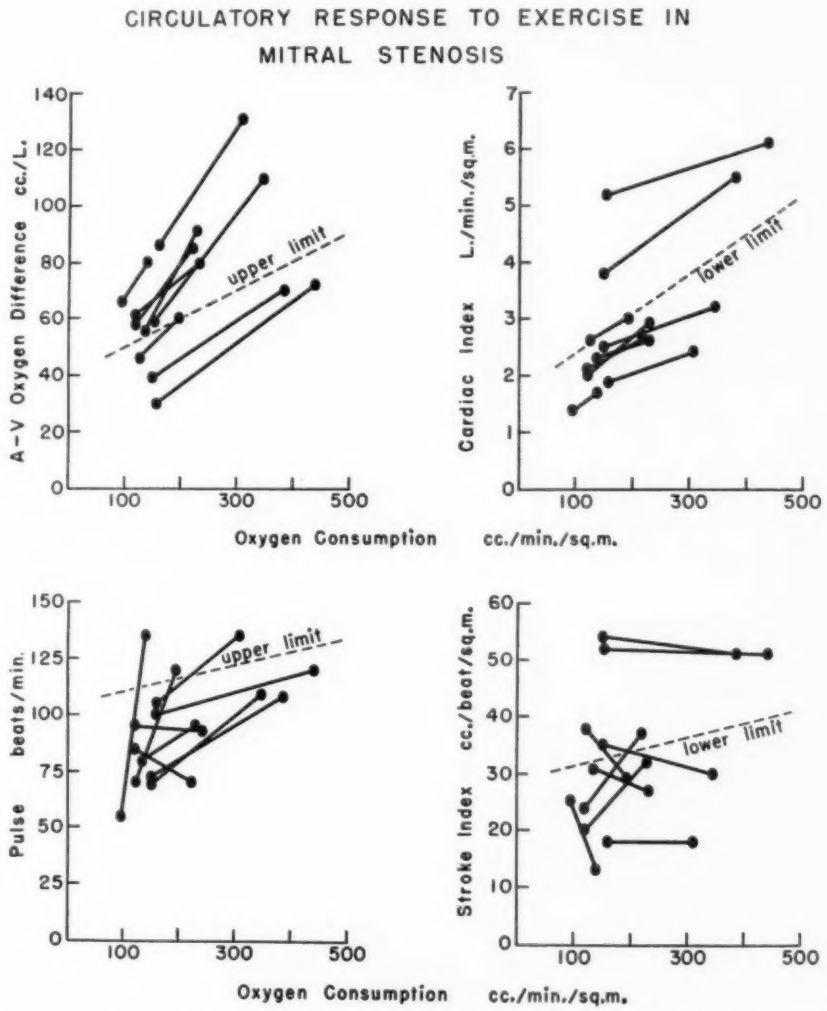

Fig. 1.—The changes in dynamics with exercise are expressed in terms of oxygen consumption per square meter. The dotted lines serve as an approximate zone of reference representing the limits of variation seen in eight normal individuals studied in this laboratory by the same techniques.[7]

Pulmonary "capillary" ("PC") mean pressure, already above normal in all patients at rest, rose much higher during the exercise period (Fig. 2). Pulmonary edema, or early symptoms thereof, occurred in three of the eight patients whose pulmonary "capillary" pressure rose to levels of 35 mm. Hg or more.

The pulmonary arterial mean pressure was elevated at rest in all patients, the values ranging from 25 to 66 mm. Hg (Fig. 2). In each, the pressure rose

further with exercise. The increment of rise, however, was commensurate with the increase in pulmonary "capillary" pressure and, in some, with the increase in blood velocity flow. As a result, the pulmonary artery-pulmonary "capillary" (PA-"PC") mean pressure gradient either remained the same or rose only 1 to 15 mm. Hg.

Consistent with small changes in output and small changes in gradient, the calculated pulmonary arteriolar resistance showed no significant change in any of the patients during exercise (Fig. 2). Any changes observed were well within the error of measurement of cardiac output and pressures by the techniques used in this laboratory.

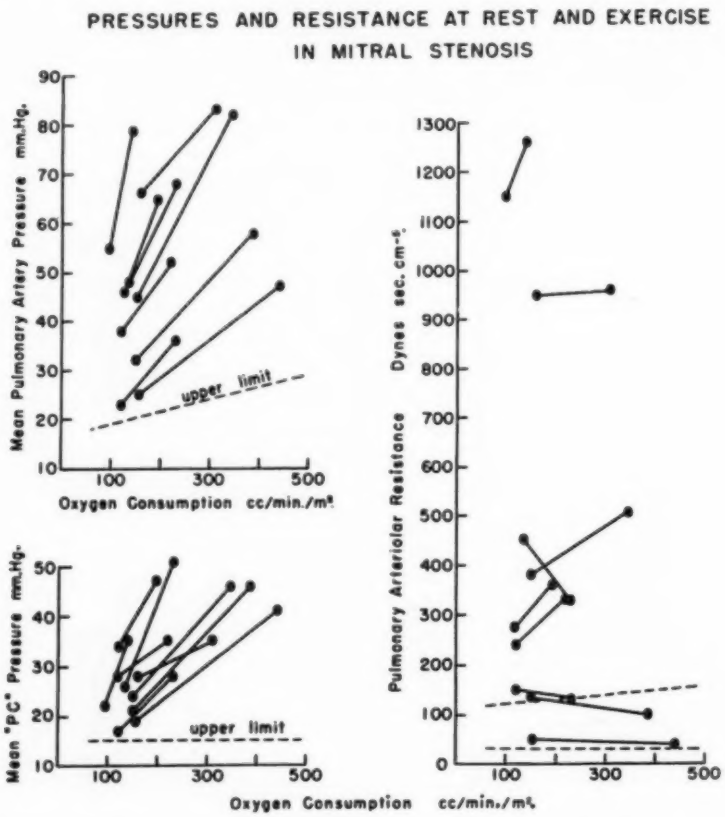

Fig. 2.—The changes in dynamics with exercise are expressed in terms of oxygen consumption per square meter. The dotted lines serve as an approximate zone of reference representing the limits of variation seen in eight normal individuals studied in this laboratory by the same techniques.[7]

Right ventricular work against pressure was elevated at rest in six of nine patients and rose further with exercise (Fig. 3). The greatest amount of work was done by the three individuals (J. F., L. T., and J. D.) who had high cardiac outputs with little pulmonary obstruction to blood flow.

Right atrial pressure was essentially unchanged in two of four patients in whom it was measured during exercise. In patient M. M., the right atrial mean pressure rose markedly. Peripheral arterial pressures on exercise were obtained

in only four patients. The pressure rose in one, remained the same in one, and fell in the other two. In these four, the total peripheral resistance decreased with exercise. Left ventricular work against pressure was unusually low at rest in these four patients and increased somewhat in only two with exercise (Fig. 3).

DISCUSSION

This small group was considered to represent all but the most severe degree of mitral stenosis. Those patients who, on rehearsal the day before cardiac catheterization, developed a marked tachycardia or symptoms of pulmonary edema with exercise were studied only in a resting state for fear of precipitating acute pulmonary edema during the actual procedure. As will be discussed later, even this type of screening failed to prevent the occurrence of pulmonary edema in some of the patients during the study.

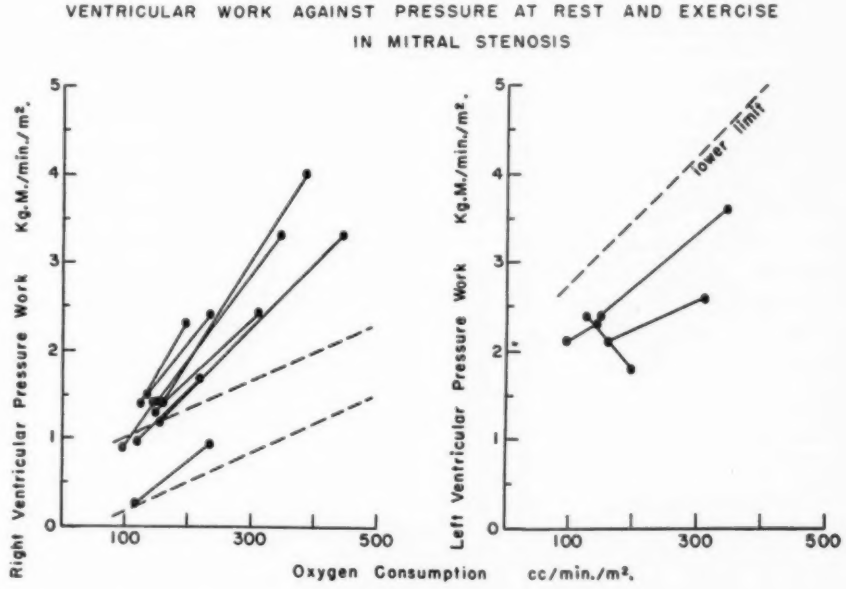

Fig. 3.—The changes in dynamics with exercise are expressed in terms of oxygen consumption per square meter. The dotted lines serve as an approximate zone of reference representing the limits of variation seen in eight normal individuals studied in this laboratory by the same techniques.[7]

It was believed, as discussed in a previous communication,[7] that oxygen consumption was a good measure of work for comparing various circulatory responses in different patients, both individually and as a group. As has been discussed elsewhere,[11] in patients with mitral stenosis peripheral blood flow (cardiac output) and pulmonary pressure come into an equilibrium at rest, such that output is somewhat lower and pulmonary pressure higher than normal. The acute increase in bodily blood flow requirements consequent on exercise tended to upset this equilibrium.

Oxygen consumption increased to variable degrees, dependent probably on three factors: (1) the actual degree of external work performed, (2) the muscular

efficiency, and (3) the circulatory ability to supply oxygen to the tissues. As was stated earlier, no attempt was made to evaluate these individual factors. As shown in Table I, oxygen consumption rose less in those who had the most severe degrees of mitral stenosis. In none of these patients was blood flow commensurate with the tissue oxygen demands. As a consequence, the tissue oxygen extraction, as expressed by the arteriovenous oxygen difference, was increased markedly in the five patients who had low cardiac outputs during exercise. Meakins and associates[1] first commented on this limited increase in cardiac output with exercise in mitral stenosis, while Hickam and Cargill[2] and Ellis and Harken[3] actually observed no increase in most of their patients. In our small group a large range of output was seen. Five of our patients had essentially fixed cardiac outputs on exercise. It is probable that three factors were responsible for this fixation: (1) the right ventricle was unable to increase its output in the face of extremely high pulmonary arteriolar resistances, especially if right ventricular failure existed; (2) the motivation for effort on the part of the patient became limited by symptoms arising from pulmonary congestion, since flow through the stenotic mitral valve could be increased only by a rise of pressure in the pulmonary circuit[14]; and (3) the decrease in stroke volume on exercise was consistent with the fixed output of the right ventricle (see preceding discussion) and the decreased periods of diastolic filling per beat caused by tachycardia.[15,16] Filling of the ventricle probably takes place during the whole of diastole in mitral stenosis. Thus, if the cardiac output is essentially fixed, any decrease in diastolic filling period as occasioned by tachycardia will result in a decreased output per beat in patients with mitral stenosis. This was observed in our patients, in whom the cardiac output failed to rise as the pulse rates increased, even though venous return was probably increased.

In every instance, pulmonary "capillary" pressure rose with exercise. It has been demonstrated that these rises have been associated with increases in the rate of blood flow through the mitral valve.[14] These rises signified an increase in pulmonary congestion. In those patients with resting pulmonary "capillary" pressures of 26 to 34 mm. Hg (E. S., N. L., and R. W.), pulmonary edema, as indicated by râles, cough, or frothy sputum, regularly occurred during three minutes of exercise. All of these patients were slightly orthopneic at rest, indicating the existence of some pulmonary congestion before exercise began. Three patients (J. D., J. F., and L. T.), whose pulmonary "capillary" pressures were less than 25 mm. Hg before exercise, had striking elevations of pulmonary "capillary" pressure by the end of the third minute of exercise but did not have pulmonary congestive symptoms. One patient (M. M.) had a pulmonary "capillary" pressure of 35 mm. Hg after one minute of exercise. As a consequence, exercise was stopped before any symptoms could be expected to appear. Explanations for the absence of clinical pulmonary edema in these last four patients, as contrasted with the others, are as follows: The patients who developed symptoms of pulmonary edema during exercise already had some pulmonary congestion at rest, as evidenced by orthopnea and, in general, higher pulmonary "capillary" pressures. Thus, gross edema easily became manifest after further elevation of pulmonary "capillary" pressure for three minutes dur-

ing exercise. Had the four patients without pulmonary edema exercised longer, pulmonary edema probably would have occurred. The duration of pressure elevation above the colloid osmotic pressure of plasma thus becomes an important factor. Other factors, such as the height of the hydrostatic pressure gradient, the rate of transudation at a given gradient, the effect of thickened capillary alveolar basement membranes on transudation, and, finally, the relation of the amount of fluid to the amount of alveolar air space, probably affect the time of occurrence of the symptoms of pulmonary edema.

Despite sudden rises of pulmonary "capillary" pressure on exercise to hazardous levels, neither the pulmonary arterial-pulmonary "capillary" pressure gradient nor the pulmonary arteriolar resistance increased, even though the gradients and resistances were already elevated in all but the first two patients (J. D. and J. F.). A compensatory increase in arteriolar resistance, therefore, appeared to become activated in response to chronic, but not in response to acute, episodes of high pulmonary venous and capillary pressures. As in systemic hypertension, the cause of the increased resistance to flow through the arterioles is presumably on the basis of a decrease in the cross-sectional area of the arteriolar bed. This decrease in area may be due to arteriolar constriction as well as to organic narrowing of the arteriolar lumen. Acute pulmonary vasoconstriction has been demonstrated experimentally in acute pulmonary embolism[17] and possibly in acute anoxia.[18,19,20] Parker and Weiss[21] and Larrabee, Parker, and Edwards[22] have amply demonstrated medial hypertrophy and necrosis and intimal hyperplasia of arterioles of the lungs in patients with mitral stenosis such that the lumina of the arterioles were markedly decreased in size anatomically.

Whether the increased pulmonary arteriolar resistance is due entirely to these anatomic changes or to functional constriction or to a combination of the two is not known. The failure of pulmonary resistance to change in response to acute elevations of pulmonary "capillary" pressure during exercise does not shed light on this problem because so little is known of its pathogenesis in this and other diseases. The nature and reversibility of the increased pulmonary arteriolar resistance is of importance with respect to mitral valve surgery.[22] If the anatomical or functional changes are not improved by widening the mitral valve orifice, the patient may remain severely handicapped on this basis alone. Preliminary observations indicate that in at least some patients, a striking regression of this resistance may occur as soon as three weeks after successful mitral valvuloplasty.

Right ventricular work against pressure increased markedly in all patients on exercise. The actual work load, however, of the right ventricle during exercise is underestimated by calculation of pressure work alone, because when cardiac output increases, the kinetic energy component may compose up to 25 per cent of the work performed[23] as compared to only 7 per cent of the work performed by the right ventricle at rest.[24] In most patients with mitral stenosis, however, cardiac output usually remains unchanged during exercise and pulmonary arterial pressures always rise. It may be assumed that the cross-sectional area of the pulmonary artery increases and, as a consequence, the velocity work probably changes little or actually may decrease. The increased work against pressure

is explained by the high pressures required to increase the blood flow through areas of high resistance. The magnitude of this work load, brought on by the slightest exertion, appears to be the main factor responsible for the eventual decompensation of the right ventricle.

Evidence for right ventricular incompetency was seen in the elevated right atrial pressures of eight out of the nine patients at rest. In none of the patients was tricuspid stenosis present.[11] With exercise and increased work, right atrial pressure rose significantly in two (L. T. and M. M.) of the four individuals in whom it was measured, although the original pressures at rest in all four were abnormal. Although the data are few, it might be suggested that right ventricular function was adequate to the task in the two who had no further rise in pressure on increasing the work load, and that right ventricular function was inadequate in the other two.

SUMMARY

1. Eight patients with mitral stenosis have been studied at rest and during exercise by the technique of cardiac catheterization. Three of the patients developed pulmonary edema on exercise.

2. The resting balance between pulmonary pressure and peripheral blood flow was upset by exercise. The imbalance was related not only to the degree of stenosis but to the ability of the circulation to increase the cardiac output.

3. Except for two patients with mild mitral stenosis, cardiac index failed to rise in normal fashion on exercise. Stroke index on the average did not change with exercise, although both increased and decreased stroke outputs were seen, depending on the pulse rate and diastolic filling period. Tissue oxygen extraction per cubic centimeter increased markedly on exercise.

4. Pulmonary "capillary" pressure rose on exercise in association with increases in rate of mitral valvular blood flow.

5. Pulmonary arterial pressure rose on exercise in association with the increase in pulmonary "capillary" pressure and in some cases with the increase in blood velocity flow.

6. Pulmonary arteriolar resistance showed no consistent change on exercise, the average values at rest and during exercise being almost identical.

7. Right ventricular work against pressure, already elevated at rest in most of the patients, became even greater on exercise.

8. Almost all patients had elevated right atrial mean pressures at rest. Further rises occurred in two of the four in whom right atrial pressure was measured on exercise.

The authors are indebted to Dr. James L. Whittenberger of the Harvard School of Public Health for the generous use of the facilities of his laboratory.

The technical assistance of Miss Libby Servello and Miss Barbara Jacobs and the secretarial aid of Miss Barbara Johnson are acknowledged.

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DISORDERS OF THE CARDIOVASCULAR SYSTEM OCCURRING WITH CATHETERIZATION OF THE RIGHT SIDE OF THE HEART

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SINCE the introduction of the venous catheter by Forssmann[1] and its use and development in this country by Cournand and Ranges,[2] thousands of well-controlled cardiac catheterizations have been done in various clinics without cardiac damage apparent even in many autopsied patients.

There are certain complications, however, which may occur during this procedure. Local and intracardiac venous thromboses, pulmonary and cerebral emboli, and cardiac arrhythmias have been observed. Fortunately, these complications are usually temporary and transient. Fatal complications associated with cardiac catheterization have been encountered rather infrequently. The medical profession has accepted this technique as a useful and valuable tool, but its use as a casual and infrequent procedure in inexperienced hands should be discouraged.

We wish to present 2 cases of arrhythmia that could be attributed to right heart catheterization and to review the various other disorders that have occurred with this method.

ANIMAL EXPERIMENTS

Kinney, Haynes, and Dexter[3] purposely exposed dogs to traumatic venous catheterization of the right auricle, right ventricle, and pulmonary artery. Postmortem examination of the endothelium, valve leaflets, chordae tendineae, and papillary muscles failed to show any recognizable pathologic lesions immediately after the procedure. No evidence of clot formation around the catheter was observed.

Ellis, Essex, and Edwards[4] have recently reported their observations on lesions after catheterization in 16 dogs. Nine of the dogs exhibited thrombotic lesions. Two of these showed mural thrombosis in the right atrium and superior vena cava. In 3 dogs lesions coexisted in the right ventricle and atrium. In the remaining 4 dogs the lesions were mural thrombi restricted to the right auricle. The right atrial thrombi were associated with necrosis of the underlying myocardium. No emboli were found in the lungs. No apparent relationship was established between the stiffness of the catheter and estimated degree of trauma on the one hand and the presence or absence of lesions on the other.

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Received for publication Sept. 11, 1950.

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Goodale and associates[5] reported on 30 autopsies following coronary sinus catheterization in dogs. Minimal subendocardial fibrosis in the right auricle was the only finding in 4 of 5 dogs sacrificed 3 to 6 weeks after catheterization. Mural thrombi and subendocardial hemorrhages were also found in the right auricle, on the right ventricle, and on the tricuspid and pulmonary valves after catheterizing the pulmonary artery or right ventricle 48 hours later. In 3 dogs, lesions peculiar to coronary sinus catheterization were found. Two had a coronary venous thrombosis and 1 a gross hemorrhage into the myocardium drained by a catheterized vein. These complications were overcome later by using a smaller catheter and inserting it only 1 to 2 cm. into the coronary sinus. No such lesions have been reported in catheterizations of the human coronary sinus.

Banfield, Hackel, and Goodale[6] catheterized the right auricle in 12 dogs with extreme precaution to prevent trauma to the heart. Five of these were free of cardiac lesions while the remaining 7 showed mural thrombi at autopsy 48 hours later. These thrombi were on or associated with the thickened band of muscle above the fossa ovalis, on the posterior surface of the right auricle, or at the base of the tricuspid valve. In 2 dogs, subendocardial hemorrhagic areas were seen. In 6 dogs, the coronary sinus was catheterized. The lesions found were small. They consisted of thrombi and small hemorrhages in the posterior wall of the sinus and in 2 instances of tiny hemorrhages in the perisinuous fat. Electrocardiograms taken before insertion of the catheter, 1 hour after insertion, and 48 hours later showed no significant difference in any dog of the series. There were isolated and short runs of auricular extrasystoles as the catheter entered the right auricle, and isolated nodal extrasystoles were almost always produced as the catheter entered the coronary sinus. No serious arrhythmias were found.

RESULTS IN HUMAN BEINGS

Bing[7] performed 50 coronary blood flow determinations on human beings with no deleterious effects. Dexter and his group[8] reported that post-mortem examinations on 10 of their patients on whom catheterization had previously been performed failed to show any demonstrable lesions of the veins, heart, pulmonary artery, or lung attributable to the passage of the catheter.

In 2 patients on whom pathologic study of the heart was made, 1 day and 2 weeks, respectively, after cardiac catheterization at the Mayo Clinic,[4] no endocardial lesions were observed.

Venous catheterization has been performed in fairly ill and often seriously ill patients with no serious effect. It has been used in patients with congestive heart failure,[9] pericardial tamponade,[10] acute hemorrhage,[11] shock,[12] anemia,[13] and penetrating wounds of the chest.[14]

The occurrence of local venous thrombosis at the site of introduction of the catheter is not common. Careful handling of the veins and tissues and frequent moistening of the catheter with saline solution as it is withdrawn and inserted forward will help prevent this. Venous spasm around the catheter at the site of

introduction can be lessened by making sure the patient is comfortable and by injecting Novocain around the perivenous tissue every 10 to 15 minutes. We have had 2 patients with superficial phlebitis of the arm veins. These were both treated successfully with local measures. There was no extension into the axillary veins.

In man, the incidence of thrombotic lesions is extremely low. Cournand and his associates[15] reported that in more than 260 catheterizations with the catheter left in place continuously for periods up to 24 hours, no unfavorable complication was encountered beyond the formation, at times, of a mural thrombus near the site of insertion of the catheter in the brachial vein. In 2 patients, both with severe burns, the catheter had been left in place over 48 hours. Both patients ultimately died as a result of the burns and were found at necropsy to have small thrombi in 1 of the great veins traversed by the catheter. In 1 of the 2 patients, a small pulmonary infarct was found. In a number of other patients post-mortem study of the gross specimen of the auricular and ventricular wall and serial section, especially of the tricuspid valve, failed to reveal any damage to the endocardium or valve leaflets.

McMichael[16] reported that in his first group of 766 cardiac catheterizations in 1947, no mishap other than occasional local venous thrombosis had been seen. In this group, the procedure was limited to auricular catheterization. One hundred and eleven of these patients came to post-mortem examination. The right side of the heart and the tricuspid valves were carefully examined in each patient. No lesions were seen which could have been attributed to the catheter. No signs of local damage or thrombus formation or other evidence of injury to the chamber walls were seen. Two hundred and nine patients were still under hospital observation and had been catheterized once, 18 had been catheterized twice, and 2 had been catheterized 3 times. Two patients developed thrombosis of the axillary veins. One of these patients died from other causes, but there were no visible resulting pulmonary emboli and the thrombosis was of an aseptic type.

Dexter[17] noted a small number of patients with phlebitis extending into the axilla after the procedure. In 2, it was thought that the patients probably had a pulmonary embolism, as indicated by hemoptysis; although the lungs were clear to roentgenogram, and there was no friction rub or other signs of pulmonary embolism or infarction other than a slight fever. There had been no previous, nor was there any subsequent, hemoptysis in these 2 patients. Both recovered promptly. In over 800 cardiac catheterizations no serious complications have been seen in Dexter's clinic. More recently, 2 cases of pulmonary infarction have occurred, presumably due to dislodgment of mural thrombi in the right auricle in patients with mitral stenosis. Both patients had uneventful recoveries.

Johnson, Wollin, and Ross[18] described a young child with polycythemia and a congenital heart defect who died 1 month after catheterization. A thrombus was found in the right auricle, inferior vena cava, and iliac and renal veins. It is not clear from the description given whether the thrombus originated at the site of introduction of the catheter in the saphenous vein, at the base of a leaflet of the tricuspid valve to which it was attached, or in both locations.

Holling and Zak[28] reported a 19-year-old boy with Ebstein's disease who developed pain in both calves 1 week after catheterization and died 10 days later with bilateral gangrene. At autopsy a partly organized thrombus was found on the septal wall of the left ventricle which the catheter had entered via an atrial septal defect. In both popliteal arteries emboli were found which presumably had originated from the intracardiac thrombosis.

Venous thrombosis is a potential hazard in patients with polycythemia. We have had no difficulty in our patients with polycythemia and increased blood viscosity. One of our patients had a hematocrit of 90 per cent with hemoglobin of 24.8 Gm. and a red blood cell count of 10,780,000. In such incidents, we use a heparinized solution of saline through the catheter continuously.

Air embolism is always a possibility. The accidental introduction of small air bubbles into the right side of the heart is apparently of no importance unless there is an abnormal communication with the systemic circulation. In the presence of right-to-left shunts, air emboli may be thrown directly into the systemic circulation. Embolization of the cerebral vessels would be the most serious hazard of this complication. In about 1,000 catheterizations at the Johns Hopkins Hospital, Bing[7] found 5 cases where air emboli occurred during the procedure. None were fatal, and the transient neurological symptoms and signs cleared quickly. McMichael[16] observed 1 patient with cyanotic congenital heart disease who developed a hemiplegia following catheterization, but this was transient and cleared within a week. Dexter[17] had a case of transient hemiplegia in a patient with a right-to-left shunt. Burchell and Wood[19] had 1 patient who developed a transient headache and weakness of the right arm and leg 20 minutes after catheterization. This cleared in 20 minutes, and there was no residual. The patient had a large venous-arterial shunt related to a posttraumatic pulmonary arteriovenous communication. It was thought to be due to a probable fibrin embolus.

Disturbances of rhythm are the most frequent and most important complications to consider.[20,27,29] Almost every type of disturbance of cardiac rhythm has been encountered. Auricular premature beats have been seen on occasion as well as nodal premature contractions. In the most complete study of electrocardiographic changes during cardiac catheterization, Goldman and associates[20] observed 50 patients under constant visual electrocardiographic control. Thirty patients showed auricular premature systoles. These were most frequent when the catheter tip appeared to be in contact with the auricular septum and particularly when the catheter was passing through an auricular septal defect. Nodal premature beats were seen in 78 per cent of the patients. Auricular tachycardia occurred in 7 patients. Auricular flutter developed in 3 patients.

Dexter and his group[8] observed 2 patients who developed transient auricular fibrillation which subsided spontaneously in the course of one-half hour. More recently, 2 other patients with transient auricular fibrillation were seen by Dexter.[17] Burchell and Wood[19] had 1 patient who developed a paroxysmal auricular tachycardia during the procedure, but the catheterization was completed without great difficulty. The tachycardia persisted following the completion of the catheterization, and normal rhythm was restored after intravenous

Cedilanid. One other patient developed auricular fibrillation during the procedure which persisted thereafter. Johnson and his co-workers[18] reported auricular tachycardia in a patient with an interauricular septal defect when the catheter passed through the opening. Two patients of Chapman's[24] developed paroxysmal auricular tachycardia which persisted for 2 and 4 hours, respectively, despite appropriate medication.

Cournand and associates[21] observed 2 cases in their studies of auricular tachycardia. In 1 patient in whom previous attacks had been noted, the paroxysm ceased spontaneously after a short time, and in the other it stopped immediately after displacement of the catheter.

Ventricular extrasystoles appear quite frequently. Dexter[17] feels that they occur in every case in which the catheter is introduced into the right ventricle. They are produced particularly when the tip of the catheter touches the wall adjacent to the tricuspid valve. We have observed them as the tricuspid valve is first entered by the catheter tip. With the withdrawal of the catheter they cease, and frequently one can get through the tricuspid valve before more occur. The catheter should never be allowed to curl up in one of the chambers. A new and stiff catheter should not be used until it has a proper flexibility. Ventricular extrasystoles also occur quite regularly when the tip of the catheter touches the wall of the right ventricle. These are usually quickly eliminated by withdrawing the catheter a few centimeters. Goldman and associates[20] observed them as the most common arrhythmia in their series, occurring in 44 patients. In numerous patients, ventricular premature systoles arose from both the right and left ventricles.

Runs of ventricular tachycardia have been encountered.[7] Cournand, Baldwin, and Himmelstein[21] observed 1 patient with an interventricular septal defect in whom the introduction of the tip of the catheter through the defect stimulated many ectopic beats of bizarre configuration and short runs of ventricular tachycardia. On the withdrawal of the catheter into the auricle, this ceased, but the patient had signs of a mild vascular collapse. The same authors stated that death was known to have occurred suddenly in 2 adult patients with cardiac disease, 1 of whom had a long history of angina pectoris. In neither instance was the catheterization performed with electrocardiographic control. They postulated that the deaths might have been due to a ventricular arrhythmia.

McMichael[15] has now performed almost 1,000 catheterizations. Only 1 fatal incident occurred, and this could not be definitely related to the catheterization technique. An elderly patient with severe coronary artery disease developed ventricular tachycardia following a full dose of digitoxin and died in a few minutes. It was felt that this was a digitalis death which occasionally occurs in such patients whether the catheter is in place or not. Numerous episodes of ventricular tachycardia have been seen by Dexter.[17]

Defining ventricular tachycardia as an uninterrupted series of 3 or more ventricular premature systoles, Goldman and group[20] observed this arrhythmia in 39 patients of their series. Three of these patients progressed into ventricular flutter. These were temporary complications. One patient progressed into ventricular fibrillation. This developed in a 10-year-old white boy who had had a

history of paroxysmal tachycardia for many years. Ventricular tachycardia developed as the catheter entered the right ventricle and quickly progressed into ventricular fibrillation. Post-mortem studies showed a greatly hypertrophied heart with no congenital defects. Microscopic examination was thought to indicate either von Gierke's glycogen storage disease or rhabdomyoma of the myocardium. This was the only fatality in Bing's clinic in almost 1,000 cardiac catheterizations.

In Wood's series[31] ventricular fibrillation developed in 2 patients and proved fatal in 1 of them, a patient with atrial septal defect, gross cardiac enlargement, and congestive heart failure.

Goldman and associates[20] reported bundle branch block in 6 of their patients during catheterization. In all of them it disappeared quite rapidly. All were right bundle branch block. Kert and Hoobler[22] observed transient complete right bundle branch block during cardiac catheterization. They postulated that in some instances pressure of the catheter against the endocardium may delay conduction in the right Purkinje plexus, in 1 of the subdivisions of the right bundle branch, or in this structure itself.

Cournand[23] reported that right bundle branch block developed as soon as the catheter was placed in the pulmonary artery. This was thought to be due to pressure on the region of the right branch of the bundle of His and could be eliminated by withdrawing the catheter.

Chapman,[24] in an attempt to demonstrate a pulmonary arteriovenous fistula, reported sudden death in a patient when Diodrast was injected through the catheter into the cardiac chambers. This case is to be reported in detail. We have observed 2 patients with interesting arrhythmias, 1 occurring during the catheterization and the other being noted the next morning after the catheter had been removed.

CASE REPORTS

CASE 1.—P. J. (B. F. H. No. 14218), a 4-year-old white girl, was referred to the Boston Floating Hospital for evaluation of a congenital heart lesion. The mother denied any infection during the pregnancy. The child had a normal birth, weighing 7 pounds, 14 ounces. There was no cyanosis noted. At the age of 5 weeks a heart murmur was first heard. Development progressed normally. In December, 1949, the child had an episode of uncontrollable epistaxis. She was admitted to another hospital and then referred to this hospital for further study.

The girl was a well-nourished and well-developed child, 39 inches tall, weighing 33 pounds. The blood pressure was 110/68 mm. Hg. There was no cyanosis or clubbing. A palpable thrill was present over the precordium, most forceful in the fourth and fifth left interspaces. A loud, Grade 4, harsh systolic murmur was present over the entire chest and transmitted to the back. Its maximum intensity was in the third and fourth interspaces to the left of the sternum.

Fluoroscopy of the chest showed the heart to be moderately enlarged. The pulmonary artery was prominent, and the pulmonary vessels showed evidence of increased vascularity. The aorta was on the left side. The electrocardiogram was normal with a vertical position of the heart. Because of these findings, a cardiac catheterization was done. The patient was prepared in the usual manner, and the catheter entered the right auricle with ease. Several attempts were made, however, before the tip could be introduced through the tricuspid valve into the right ventricle. During this time, occasional premature beats of ventricular origin were seen as the tricuspid valve was approached. When the catheter entered the right ventricle and touched the endocardial wall, premature contractions were again seen. The pulmonary conus and pulmonary artery were entered, and the usual studies were made. As the catheter was pulled back to the right ventricle, a sudden run of supraventricular tachycardia was seen with the direct-vision elec-

trocardiogram. The catheter was withdrawn into the right atrium, and the tachycardia disappeared. It was then again introduced into the right ventricle. The tachycardia again started, and the catheter was withdrawn to the superior vena cava. The tachycardia continued for several minutes (Fig. 1). The patient's blood pressure at the beginning of the procedure was 110/68 mm. Hg. After 20 minutes the arrhythmia still persisted. Her blood pressure was 100/70 mm. Hg. After 30 minutes the patient's general condition was unimproved, and she showed pallor, increased respirations, and profuse perspiration. Carotid sinus pressure and ocular pressure produced no noticeable effect. One c.c. of a 1 per cent procaine solution was injected with no effect on the tachycardia. This was repeated twice more at 5 minute intervals. Two c.c. of a 2 per cent procaine solution were then injected directly into the catheter with the tip lying in the superior vena cava. The tachycardia ceased abruptly, and the patient's general condition immediately improved (Fig. 1). Her blood pressure again became 110/68 mm. Hg. She returned to the ward and remained free of all symptoms. An electrocardiogram the next day was within normal limits. The results of the study were compatible with the diagnosis of an interventricular septal defect.

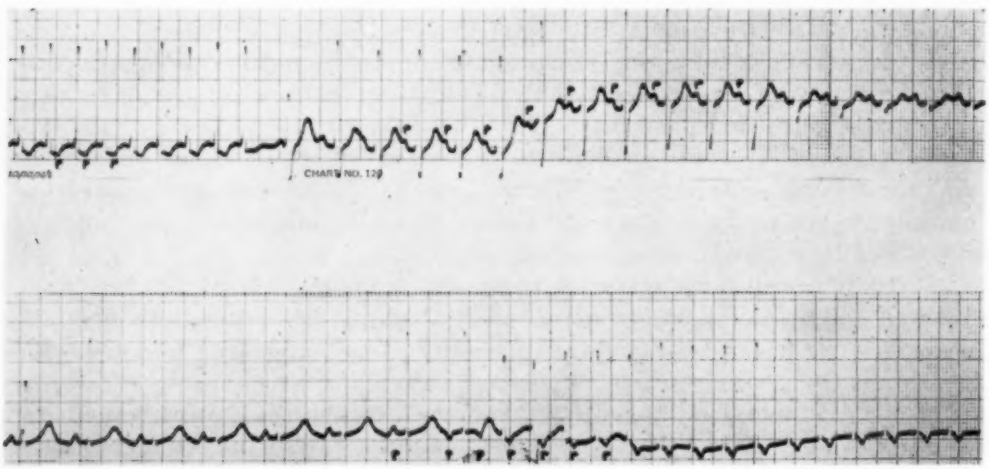

Fig. 1.—The bottom strip (Lead II) shows the sudden onset of a lower nodal tachycardia. The upper strip shows the cessation of the tachycardia after the injection of 2 c.c. of a 2 per cent solution of Novocain.

CASE 2.—J. L. (B. F. H. No. 13871), a 4-year-old white boy, was admitted to the hospital for the evaluation of a congenital heart anomaly. The child weighed 8 pounds at birth. There was no cyanosis noted. His mother had no history of infection during the prenatal period. At 1 month of age a cardiac murmur was heard. At the age of 1½ years, the mother first noted cyanosis of the lips. She stated that the child tired easily after this and was unable to climb stairs without becoming exhausted, cyanotic, and dyspneic. When he cried or became upset, he turned "stone black." Since August, 1949, a nonproductive cough had been present.

The boy was well developed and well nourished. There was marked cyanosis of the mucous membranes and nail beds with severe clubbing. The heart rate was 120 beats per minute. There was bulging of the left side of the chest. A slight thrill was felt over the third left interspace, and a Grade 2 systolic murmur was heard in the same area. The lungs were clear. Laboratory data showed a red blood cell count of 8.9 million, hemoglobin 25.2 Gm. (162 per cent), and a hematocrit of 82 per cent. An electrocardiogram showed right ventricular hypertrophy (Fig. 2).

Because of a moderately enlarged heart, it was decided to carry out right-sided cardiac catheterization. On October 31, the right arm was used first because of the better appearing veins. However, we were not able to pass the catheter into the superior vena cava. The left arm was then used, and the catheter was threaded freely to the right auricle. Several attempts were made before the catheter passed through the tricuspid valve. A few premature beats were seen, but no bundle branch block was noted. Just beyond the tricuspid valve, some resistance to the passage of the

catheter was noted. It was withdrawn slightly and then reinserted. After several attempts it entered the right ventricle freely, and further studies were carried out. The catheter entered the pulmonary artery. Pressure studies were consistent with the diagnosis of a pulmonary artery stenosis. The patient returned to the ward in good condition. No abnormalities in the electrocardiogram had appeared.

The following morning the child was restless, and his color appeared pasty. His temperature was 100.2° F., pulse 60, and respirations 48 per minute. The electrocardiogram showed a complete auriculoventricular heart block. Unfortunately, the most representative tracing of this was misplaced. The electrocardiogram reading* was as follows: "The auricular rate is 130 per minute;

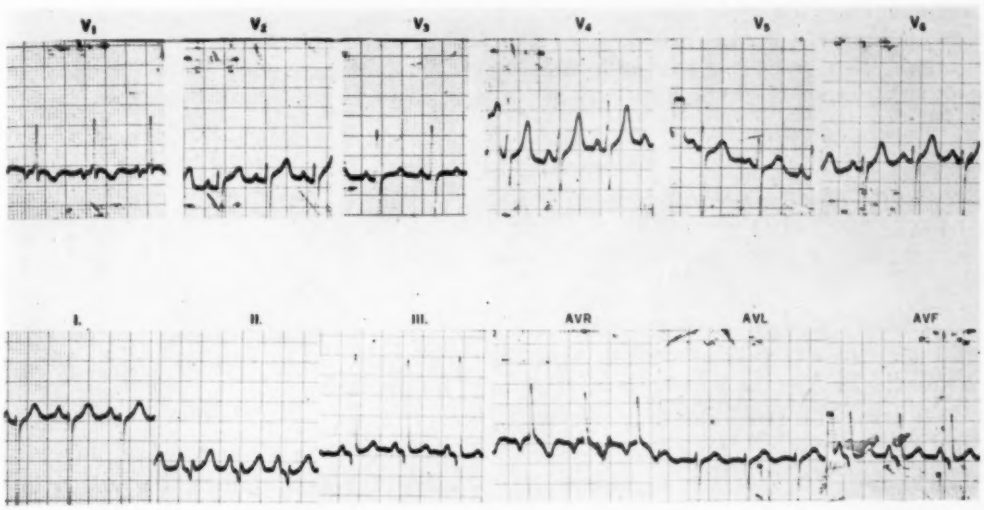

Fig. 2.—An electrocardiogram taken on admission to the hospital shows right ventricular hypertrophy. Note the upright T waves in the chest leads V_2 to V_6.

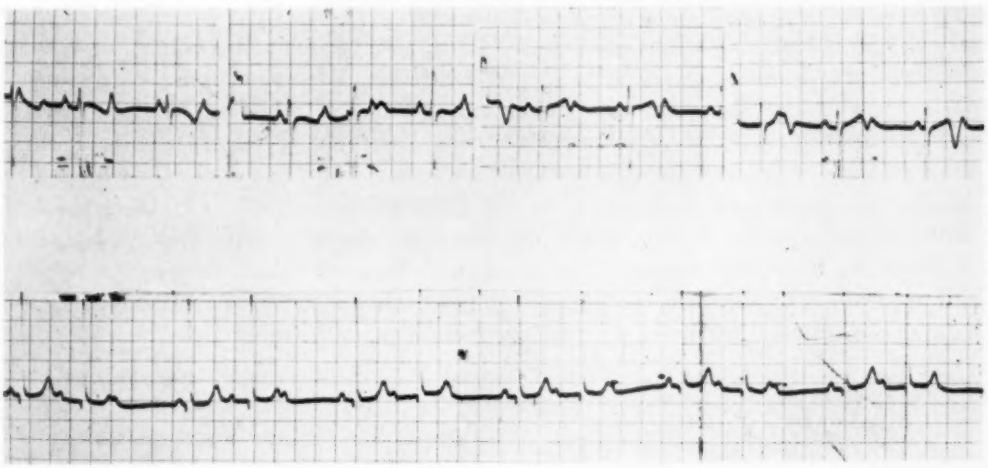

Fig. 3.—The upper strip shows the chest leads V_3, V_4, V_5, and V_6 taken November 2. Incomplete auriculoventricular heart block is present. The auricular rate is 136 per minute, and the ventricular rate is 76 per minute. The bottom strip (Lead III) was taken the next day (November 3). It shows incomplete auriculoventricular heart block with Wenckebach's periods.

*Read by Dr. Heinz Magendantz, Chief of Cardiac Clinic, New England Center Hospital.

ventricular rate is 104 per minute; the T wave is inverted in V_1, V_2, V_3, V_5, and V_6. The tracing shows complete A-V heart block and evidence of myocardial damage."

The next day, November 2 (Fig. 3), a tracing showed an incomplete heart block. The auricular rate was 136, and the ventricular rate was 76 beats per minute. On the following day, November 3, incomplete heart block was present with periods of Wenckebach's phenomenon. The auricular rate was 125, and the ventricular rate 85 per minute. The T wave in V_1 and V_2 was still inverted, but it was now upright again in the other chest leads.

By the seventh day, the electrocardiogram had returned to normal. The child had improved clinically. He was subsequently operated upon,* and findings confirmed the preoperative diagnosis of a tetralogy of Fallot. An aorta-pulmonary artery anastomosis was performed. After a normal postoperative course, the child was discharged markedly improved. He was seen 2 months later, and his mother stated that the child's physical capacity had increased beyond her fondest dreams. His cyanosis had practically disappeared. A repeat electrocardiogram showed right ventricular hypertrophy with a normal sinus rhythm. No evidence of heart block was present.

COMMENT

This temporary complication appeared first the day following the procedure. It may have begun several hours before this, as the patient's pulse was found to be irregular the evening of the catheterization. It is quite possible that the bundle of His was injured temporarily. It could be postulated that a small subendocardial hemorrhage occurred such as was observed in dogs by Goodale and associates.[5] All evidence of heart block disappeared in 7 days. A follow-up 2 months and again 4 months later showed no abnormality.

Ferrer and co-workers[25] observed 1 case of temporary complete heart block in a recent report. Two other cases were cited in which a vasovagal syndrome developed. In 1 of the 3 patients, the circulatory disturbance seemed to be associated with the handling of the arterial needle, either at the time of insertion or at the time of removal. In none of these 3 patients was the catheter in place, either because it had been removed or because it had not yet been inserted.

Various degrees of auriculoventricular block developed in 4 patients of the series reported by Goldman and group.[20] First-degree auriculoventricular block was seen in 2 patients. Complete auriculoventricular dissociation developed in a patient with tetralogy of Fallot. This quickly disappeared on withdrawal of the catheter to the superior vena cava. Another patient with tetralogy of Fallot presented all 3 grades of auriculoventricular block. Complete auriculoventricular dissociation occurred with the catheter tip in the inflow tract of the right ventricle. With the catheter in the superior vena cava, auriculoventricular dissociation was replaced by a second-degree, then by a first-degree auriculoventricular block, and finally by normal sinus rhythm. None of these instances of auriculoventricular block interfered with the completion of the cardiac catheterization.

DISCUSSION

Catheterization of the right side of the heart has rapidly become a standard, useful tool in competent hands for the study of congenital heart disease and other cardiovascular diseases in man. There are potential hazards to the method, but, fortunately, most complications that have been observed during or after completion of cardiac catheterization are of a minor character. Stead[26] has done

*By Dr. C. Stuart Welch.

approximately 1,200 catheterizations with no serious complications. The incidence of thrombotic lesions in human beings is low as compared to that in dogs. The fact that mural thrombi and other cardiac lesions following cardiac catheterization have not been found in man except in the cases reported by Johnson and co-workers[18] and Holling and Zak[28] has been postulated by Banfield and associates[6] to be due to several factors. Thrombi may not occur because the clotting mechanism in man is less active than in the dog. The catheter may cause less abrasion in the less active human heart, which lies within a more fixed mediastinum and beats at a much slower rate than the dog's heart under Nembutal anesthesia. Also, the band of auricular muscle above the fossa ovalis in dogs is less prominent in man. These authors stated that at least 30 human patients have been observed at autopsy, following postoperative death, in the clinics of Cournand, Bing, and Dexter only a few days after cardiac catheterization. There was no evidence of damage from this method in any of the hearts.

These potential lesions must be borne in mind and investigated when they do occur. Most of the complications can be avoided by careful and meticulous observance of proper technique. The patients must be made comfortable on the table. The local area of insertion should be freely infiltrated with Novocain and careful handling of the tissues and veins observed. Special care should be taken when the arterial needle is inserted, manipulated, or withdrawn.

The catheter should never be advanced against resistance, be allowed to curl up on itself, or to buckle in the heart chambers. Above all, the procedure should always be done under electrocardiographic and fluoroscopic control. With the patient attached to the electrocardiograph, all arrhythmias can be recognized immediately and proper therapy instituted. Direct-vision machines are preferred.

The catheter should not be allowed to remain in the right ventricle longer than necessary to draw the desired blood samples. It is also recommended that one should use very gentle negative pressure on the syringe when withdrawing blood from the right ventricle.

It is practically impossible to catheterize without inducing premature beats. These may be reduced by the use of quinidine[31] or procaine given intravenously.

Cournand and associates[15] stated that no injections should be made through the catheter directly into the heart except for nonirritant fluids, such as saline, plasma, or whole blood. Even a slow infusion of 200 c.c. of saline solution precipitated failure in one case of buttonhole mitral stenosis.[16]

In patients with increased blood viscosity and polycythemia, venous thrombosis is an increased hazard. The use of heparinized saline solution should be helpful. Whether or not anticoagulants should be continued after the catheter has been withdrawn has not been definitely established. The catheter should be cannulated and cleaned immediately after it is withdrawn to remove small blood clots clinging to the sides of the catheter and to prevent a pyrogenic reaction or embolus in the next patient. Penicillin should be given to the patient before and after the procedure for prevention of any potential infection, although none have been reported.

I am indebted to Professor J. McMichael for the data collected from the major centers in England appearing in Table I. McMichael[16] in his own series had 3 patients develop anginal pain, and 2 of these had definite coronary thromboses following the procedure. In all, the catheter had entered the coronary sinus. Precordial pain, slight fever, and electrocardiographic changes regarded as characteristic of pericarditis developed in 1 patient in whom a rather stiff catheter had entered the coronary sinus.

In England, McMichael[16] deplored the "occasional" catheterization done in "provincial" hospitals. He felt that most of the serious complications would come from this source. The same can be emphasized here in this country. The procedure is not without danger, particularly in congenital heart disease. As increasing numbers of investigators are preparing to do catheterizations, it is well that they are made aware of its potential and real dangers. Isolated and infrequent catheterizations should be discouraged. There have been 11 deaths reported or mentioned in the literature.[16,18,20,21,24,27-31] Six of these were associated with the catheter in situ.

TABLE I

	McMICHAEL (POSTGRADUATE SCHOOL SERIES)	WOOD* (NATIONAL HEART HOSPITAL SERIES)	SCHAFER (ST. THOMAS' HOSPITAL SERIES)	HOLLING* (GUY'S HOSPITAL SERIES)	DEUCHAR† (GUY'S HOSPITAL SERIES)	TOTAL
Number	995‡	225	160	70	70	1500
Complications						
Thrombosis of axillary veins	4	0	0	1	1	6
Embolism, pulmonary or systemic	1	0	1	3	0	5
Precipitation of left heart failure	9 (1 fatal)	1§	2	0	0	12
Deaths with catheter in situ	1	1	0	0	0	2
Other Sequelae	2 coronary thromboses, 1 pericarditis of uncertain causation (all recovered)	2 meningocerebral symptoms, ? due to embolism (1 recovered, 1 died); 1 anginal pain		1 meningovascular		7

*Mainly congenital hearts.[28,31]
†Series in addition to those already reported by Holling and Zak.[28]
‡In 766 of these the catheter was in the right atrium only.
§Paroxysmal tachycardia with unconsciousness: recovered.

There have probably been more deaths that have not been reported or revealed in this present study. Many investigators have come to regard the procedure as a relatively benign one. I, for one, have developed a constant healthy fear of the right ventricle and feel that anyone engaged in doing cardiac catheterization certainly must share this viewpoint. The procedure still needs a well-trained team, and, as has been stated before, most complications can be avoided by the experience of this team with its strict adherence to the proper technique.

As has been emphasized by Goldman and associates[20] and Michel and co-workers,[27] arrhythmias are the most common and serious complications that occur. The latter group reported on 113 consecutive venocardiac catheterizations. Abnormal rhythms developed in more than one-third. The tendency was significantly greater in the presence of congenital heart lesions and in patients whose electrocardiograms were abnormal prior to the procedure. These observations are in line with certain cardiovascular abnormalities which should be considered definite contraindications to the procedure. Dexter[17] listed them as follows: spontaneous ventricular extrasystoles, recent history of paroxysmal ventricular tachycardia, subacute bacterial endocarditis, coronary occlusion within 6 weeks, any manifestation of digitalis toxicity (especially bigeminy), diffuse myocarditis (e.g., rheumatic), and auricular fibrillation.

SUMMARY

Two patients showing temporary complications with catheterization of the right side of the heart have been presented. One developed a nodal tachycardia with the catheter in place. The arrhythmia did not cease spontaneously after 30 minutes and was terminated by treatment. The other patient with a tetralogy of Fallot developed complete auriculoventricular heart block 1 day after the catheter had been removed. Second-degree heart block then appeared, followed by first-degree auriculoventricular heart block, and finally the electrocardiogram returned to normal in 7 days.

The literature has been reviewed, and results in other clinics have been presented. Catheterization of the right side of the heart has proved to be a most valuable aid in the diagnosis of congenital heart disease and in the study of other heart and pulmonary diseases. It has an established place in the hands of competent investigators, but successful application of this technique still needs a trained team who by careful and meticulous observance to proper technique and certain contraindications can avoid most fatal complications.

I wish to express my extreme appreciation to Dr. Lewis Dexter for his many helpful comments and suggestions in the preparation of this manuscript.

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TRANSIENT RIGHT BUNDLE BRANCH BLOCK PRODUCED BY HEART CATHETERIZATION IN MAN

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THE diagnosis of bundle branch block in man is based essentially on extensive experimental work in dogs.[1-3] Occasionally, lesions of the bundle branches have been found at post-mortem examination in patients who exhibited bundle branch block pattern during life,[4,5] but such cases are rare compared to the large number of patients in whom the diagnosis is made without eventual verification at autopsy. Moreover, the importance of this earlier material has been recently questioned by Glomset and Birge,[6] who claim that the bundle of His does not exist in man as it does in some animals. In an analysis of 114 cases, these authors found diffuse fibrosis in the upper part of the septum, but, as a rule, no preponderance of damage on one or the other side of the septum could be seen, so that the bundle branch block pattern (right or left) seemed to have been determined by the pre-existing preponderance. This finding is in agreement with the study of Rasmussen and Moe,[7] who found that in 100 patients with left bundle branch block the electrocardiographic finding was accounted for 5 out of 6 times by enlargement of the left ventricle instead of by any local septal lesion. We should also note the observation that the development of bundle branch block (right or left) is associated with a significant axis shift (exceeding 15 degrees) in the minority of cases.[8]

In addition to these questions concerned with the pathological background, the electrocardiographic differentiation between complete and incomplete bundle branch block and ventricular strain patterns is not always clear. For instance, we have found that electrocardiograms like those published by Barker and Valencia[9a] in their Fig. 7,*B* and *D*, as examples of incomplete bundle branch block were not uncommon in 400 normal men.[10] Both of the "patients" reported by Barker and Valencia were clinically normal.

In view of this situation, the experimental (though unintentional) production of transient bundle branch block in man has unusual interest. Only one similar experiment (on a dog) has been reported in the literature on electrocardiography[2]; this will be discussed later.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

This work was supported in part by the Research Grants Division of the United States Public Health Service.

Received for publication Aug. 1, 1950.

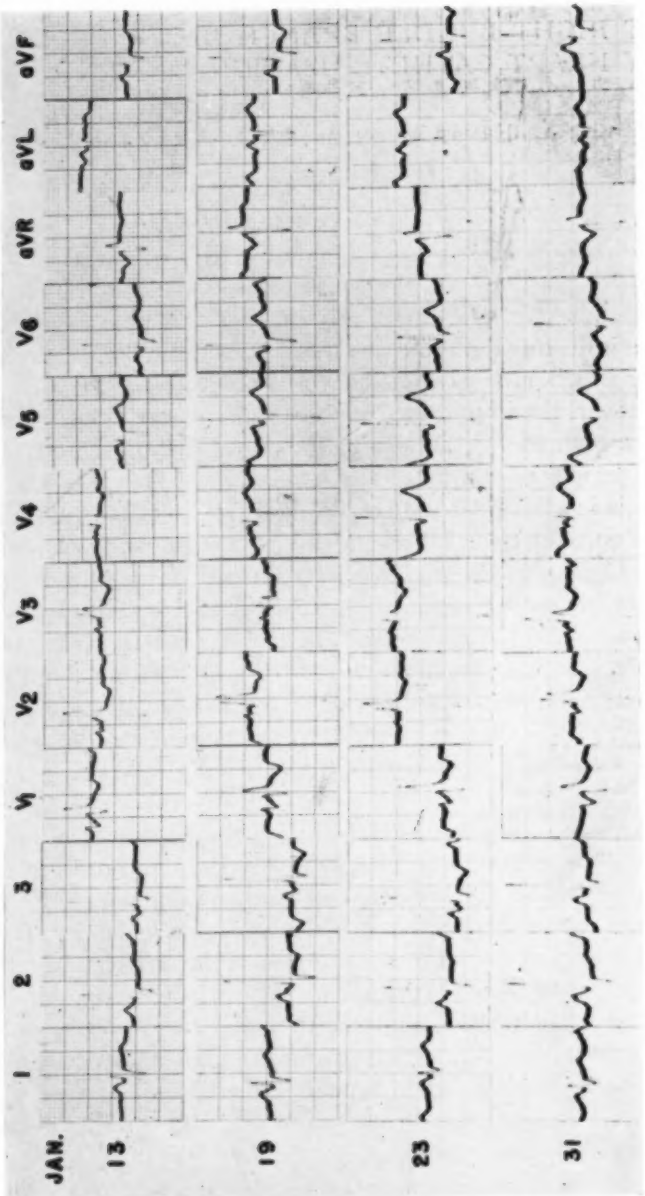

Fig. 1.—Twelve-lead electrocardiograms before catheterization (January 13), 3 hours after catheterization (January 19), and 4 days (January 23) and 12 days (January 31) after catheterization. Slow recovery of T inversion in Leads II, III, and aV_F.

METHOD

The heart catheterization was performed by Dr. R. V. Ebert, Dr. C. Borden, and Dr. R. Wilson. Electrocardiograms (3 limb leads, V_1 to V_6 inclusive, aV_R, aV_L, and aV_F) were taken 6 days before and again immediately before catheterization. During and after catheterization, electrocardiograms, mostly the 3 standard leads, were taken at frequent intervals. After catheterization, electrocardiograms from the left and right sides of the chest were obtained in continuous sequence for a period of about 85 minutes, followed 2 hours later by another 12 lead electrocardiogram. Two additional 12 lead electrocardiograms were taken 4 and 12 days after the catheterization. In all records the amplitude was standardized at 1 mm. = 0.1 mv.

The patient was a 50-year-old man with a history of rheumatic heart disease and mitral insufficiency and stenosis. He had been admitted to the hospital in a state of cardiac decompensation 8 days before catheterization and had improved considerably during that time. The right ventricular and pulmonary diastolic pressures were found to be increased to 5.8 and 38 mm. Hg, respectively.

RESULT

The electrocardiogram taken 6 days before catheterization (Fig. 1, January 13) showed a right ventricular strain pattern in the standard leads with a QRS interval of 0.10 second. V_1 and V_2 showed a late R′ preceded by a deep S wave and could be interpreted as incomplete right bundle branch block probably combined with right ventricular preponderance, using the criteria of Myers and associates,[9b] and Barker and Valencia.[9a] The electrocardiogram taken immediately before catheterization (Fig. 2, first row) was substantially identical.

In the attempt to catheterize the right ventricle, the catheter came in contact with the right septum and was immediately withdrawn. The electrocardiogram taken 1 minute later showed a typical right bundle branch block pattern with a QRS interval of 0.13 second (Lead III, Fig. 2). Heart catheterization was resumed, and pressure readings of the right cavity and the pulmonary artery were obtained later. The right bundle branch block persisted for a period of 1 hour, as shown, for example, in electrocardiograms taken 5, 25, 40, and 60 minutes after the contact with the septum was made. It is of interest that the heart rate remained constant and regular throughout, no extrasystoles being observed. Fig. 3 (first row) shows the right bundle branch block in aV_R, aV_L, and aV_F 60 minutes after the lesion.

Ten minutes later, a rather rapid recovery took place with regular phasic variations of QRS amplitudes and intervals (Fig. 4). Fig. 4 shows 4 cycles in Leads V_1, V_4, V_{4R}, and V_{5R} and 2 cycles in Leads V_2, V_3, V_5, and V_6. The length of the phases varied within narrow limits of about 3 beats. The change between wide and narrower QRS intervals was gradual rather than abrupt. The change of the amplitudes, especially in leads facing the right ventricle (V_1, V_{4R}, and V_{5R}), far exceeded the variation of the QRS interval, which is consistent with some of the observations of Barker and Valencia.[9a] In Lead V_1 the wider complexes showed a much larger, late intrinsic deflection and only an

embryonic S wave as compared to the electrocardiogram before catheterization (Fig. 1, first row). The T wave was deeply inverted. The narrower complexes had a smaller R′ and a somewhat larger S wave and a smaller inverted T wave, approaching but not attaining the pattern of the QRS complex before catheterization.

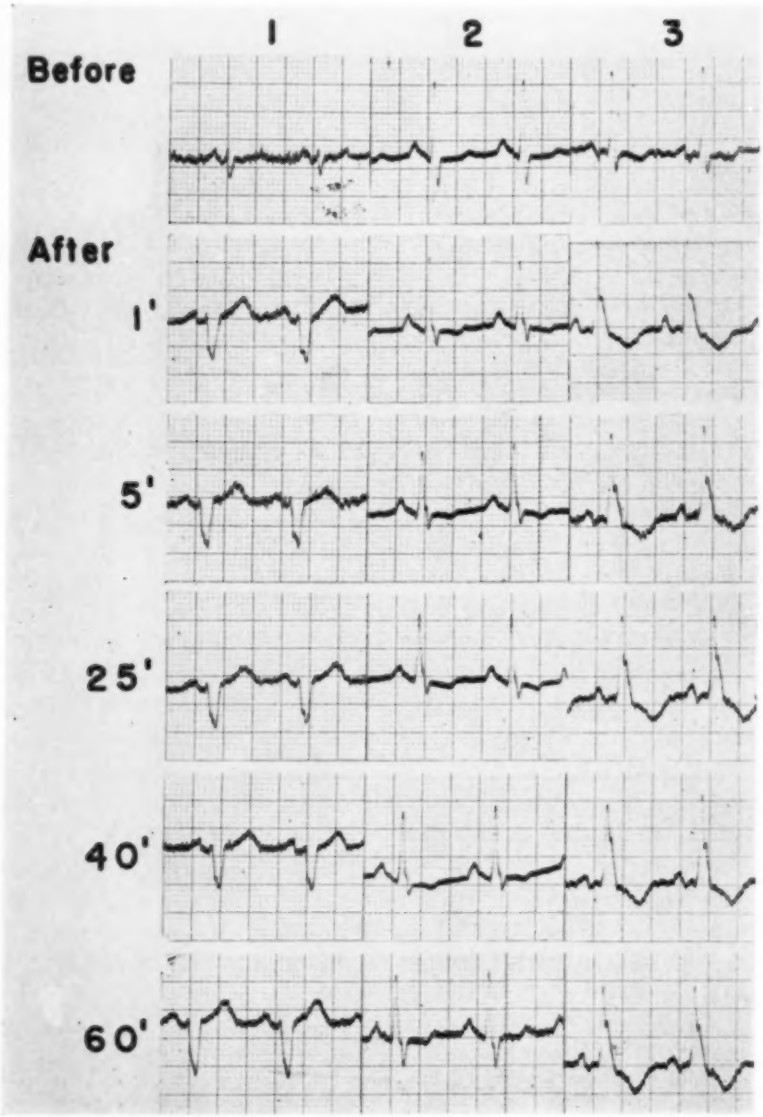

Fig. 2.—Right bundle branch block, appearing immediately after catheterization (*1'*), persists with little change for 1 hour (Leads I, II, and III).

In Leads V_2 to V_6 with an S wave as the major deflection, the second nadir of the notched S wave in the wide complexes seemed to correspond in time to the peak of R′ in V_1. The difference between the wider and narrower QRS complexes

in these leads consisted in the presence or absence of the second nadir; the initial R wave and the first part of the S wave were identical. The T waves were larger in the wide QRS complexes. In Leads V_{4-6} the initial R wave was much smaller both in the narrower and wider complexes than in the electrocardiogram before catheterization (Fig. 1, first row). The S wave in V_6 (Fig. 4) was much larger than that before catheterization, thus simulating the picture of a different position of the heart (clockwise rotation around the long axis).

While in all leads taken 70 to 80 minutes after the lesion wider and narrower complexes alternated in regular sequence, the QRS interval showed an over-all trend toward shortening, so that in Leads V_{4R} and V_{5R} (taken about 80 minutes after the lesion) the QRS interval was below 0.12 second, even in the wider complexes.

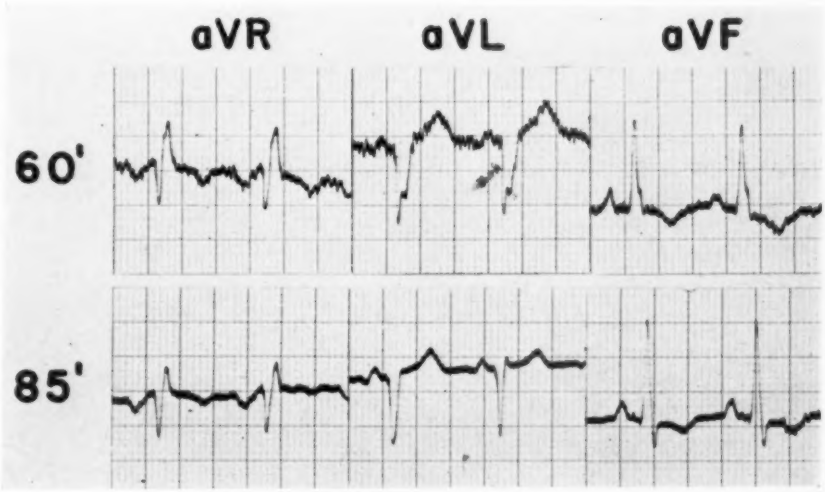

Fig. 3.—Right bundle branch block in the unipolar limb leads 60 minutes after the lesion (first row); recovery after 85 minutes (second row).

Eighty-five minutes after the lesion, Lead I, here shown as Fig. 5, was the last record to show these variations between narrower and wider complexes. The QRS interval in the wider complexes was 0.10 second and that of the narrower complexes was 0.08 second, identical with that before catheterization (Fig. 1, first row). However, the QRS complex was more inverted. The QRS complex in Leads II and III was similar to that before catheterization, but the T wave was inverted. The T wave was also inverted in Lead aV_F (Fig. 3).

One hour later, i.e., 2½ hours after catheterization, a 12 lead electrocardiogram showed QRS complexes similar to those before catheterization, except for a deeper S wave in V_6, but the T wave in Leads II, III, and aV_F was still inverted (Fig. 1, second row). Four days later (January 23), the S wave had decreased to its original amplitude, but the T wave did not recover before the next repeat electrocardiogram 1 week later (January 31).

DISCUSSION

The fact that a transient right bundle branch block could be produced by catheterization is not compatible with Glomset and Birge's claim that His'

bundle is absent in man. However, this does not disprove the possibility that a bundle branch block pattern may be produced by a more diffuse involvement of the ventricular wall.

The rate of alternating wider and narrower QRS complexes during the recovery (70 to 85 minutes after the lesion) corresponded with the average respiratory rate of the patient. Although no record of respiration was made, the interpretation of these variations as respiratory cycles seems to be most probable.

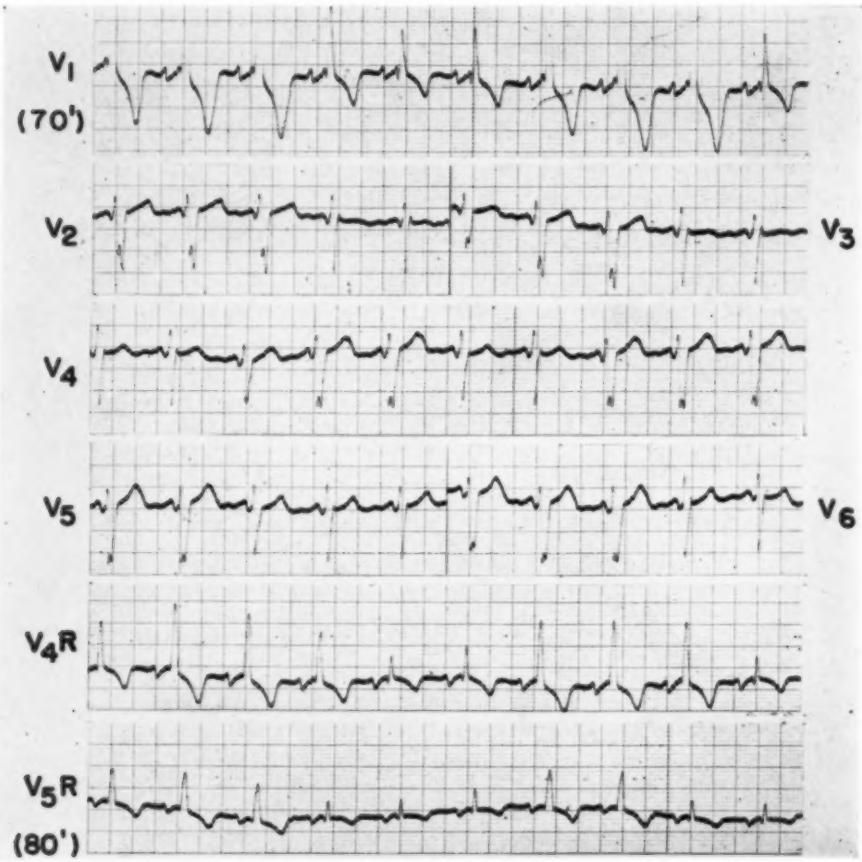

Fig. 4.—Recovery phase in 8 precordial leads from 70 to 80 minutes after the lesion. Phasic variations of width and amplitudes probably correspond to respiratory cycles. There is a gradual trend to shortening of the QRS intervals, but the variations are still present in V_{4R} and V_{5R}, when the QRS interval has approached normal values.

Changes of ventricular conductivity with the tone of the vegetative nervous system, including respiratory variations, have been observed by Nichols[11] in a case of right bundle branch block. It is of interest that the conductivity of the right bundle branch was affected through the respiratory cycles (or other cycles of unknown origin) only during the phase of recovery and not during the phase of complete block or after recovery.

The variations of the amplitude exceeded in magnitude the concomitant variations of the QRS interval. The amplitudes of the wider QRS complexes were larger, which should be expected from the different pathway of ventricular

conduction. However, the changes of the amplitudes in the Leads V_1, V_{4R}, and V_{5R} from wider to narrower complexes were gradual, and also large variations of the amplitude occurred when the total QRS interval was shorter than 0.12 second (V_{4R} and V_{5R}). This is not compatible with the assumption[9a] that in incomplete bundle branch block the conduction is delayed only in the bundle while the ventricular activation proceeds normally. It appears that a certain degree of aberration of ventricular conduction occurs in incomplete bundle branch block, though to a lesser extent than in complete bundle branch block. The difference between complete and incomplete bundle branch block is probably quantitative rather than qualitative.

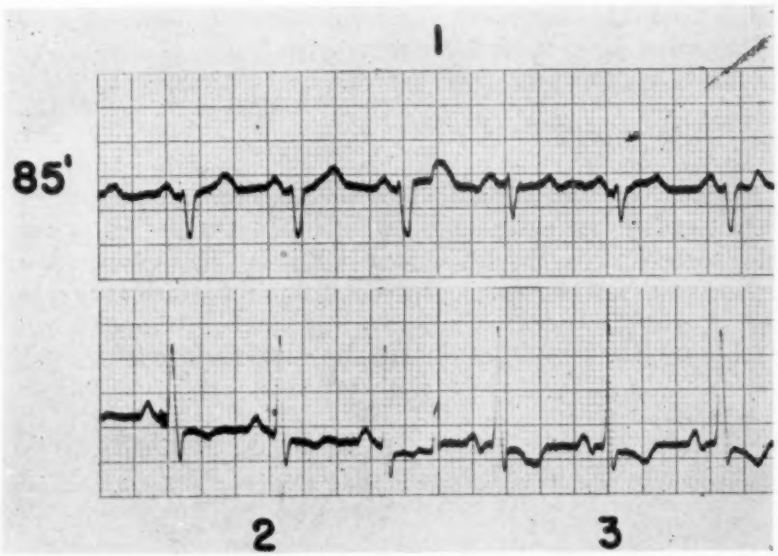

Fig. 5.—Phasic variations in Lead I 85 minutes after the lesion (first row); disappearance of phasic variations in Leads II and III (second row), taken immediately after Lead I. T inversion in Leads II and III.

Comparing the narrower complexes in Leads V_3 to V_6 in Fig. 4 with the same leads before catheterization in Fig. 1 without knowledge of the production of a transient right bundle branch block, an interpretation of the development of rather extreme clockwise rotation of the heart after catheterization would have been made. The narrower complexes were within normal QRS interval limits. Since the position of the heart certainly did not change during the experimental period, the deep S wave in the leads from the left side of the chest must have been due to a different pathway of ventricular conduction, even in the absence of detectable conduction delay.

Our observations corroborate the findings in 1 experiment on a dog by Rothberger and Winterberg.[2] These authors produced a transient right bundle branch block by quite heavy pressure with the blunt side of a knife in the region of the right bundle. The block appeared for a few minutes. During its gradual disappearance, the previously positive QRS complex in the esophagus-rectal lead remained inverted, even when the QRS interval approached the pre-experimental values. It is of interest that 2 hours after the lesion in our patient the

S wave in V_6 was still much larger than before the catheterization (Fig. 1). Obviously, it is advisable to be conservative in the interpretation of the "electrical position" of the heart by means of unipolar chest and limb leads.

Another point of interest is the fact that heart catheterization by a team with an experience of over 200 catheterizations produced this lesion, from which the patient did not recover for several days. Harvey and associates[12] mentioned transient right bundle branch block in 2 of their patients during heart catheterization, though no electrocardiographic analysis was made. Meanwhile, the same lesion was seen in a third patient.[13] After the completion of this manuscript, 2 more cases of transient right bundle branch block were published by Ravin and co-workers[15]; however, no detailed electrocardiographic analysis was made. It appears that production of right bundle branch block by heart catheterization might not be rare, and even more serious lesions such as ventricular fibrilllation have been occasionally observed.[14] This emphasizes the necessity of caution and careful selection of patients for heart catheterization.

SUMMARY

In a patient with pulmonary hypertension and right ventricular strain pattern, heart catheterization produced transient complete right bundle branch block (QRS interval, 0.13 second) which persisted for 1 hour and was followed by gradual recovery during the next 20 minutes. During the recovery period, alternating phases of wide and narrow QRS complexes were observed. In spite of the recovery of the ventricular conduction time, several changes (T-wave inversion in Leads II, III, and aV_F; S wave in V_6) did not disappear before several days. Theoretical and practical consequences are discussed.

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PROGNOSIS IN BUNDLE BRANCH BLOCK

II. Factors Influencing the Survival Period in Left Bundle Branch Block

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IN A previous communication the factors influencing the survival time in right bundle branch block were analyzed. The purpose of this paper is to analyze in a similar fashion a consecutive series of 555 patients showing the electrocardiographic pattern of left bundle branch block.

METHOD OF STUDY

The present series consists of 555 patients in whom the electrocardiographic diagnosis of left bundle branch block was made in the Cardiac Laboratory of the Massachusetts General Hospital, Boston, Mass., during the years 1937 to 1948 inclusive. All of the electrocardiograms had a QRS interval of 0.12 second or greater. Prior to 1943, precordial leads were not taken routinely; during that period the criteria for diagnosis included a QRS complex of 0.12 second or greater, a broad R wave in Lead I, and the absence of a broad S wave in Lead I. Since 1943, when multiple precordial leads became routine, the criteria have been more definite and include, besides a QRS duration of 0.12 second or more in the bipolar limb leads, the following: a broad-topped, bifid, or notched R wave in leads over the left ventricle and a broad S wave in leads over the right side of the precordium. The intrinsicoid deflection was not measured as such but was always shown to be late in complexes recorded over the left ventricle.

The following types of electrocardiograms were excluded from this study: complete heart block, short P-R intervals (Wolff-Parkinson-White syndrome), tachycardia (over 100 per minute) (in order to eliminate both paroxysmal ventricular tachycardia and supraventricular tachycardia with aberrant conduction), transient or paroxysmal bundle branch block, and incomplete or indeterminate bundle branch block. All patients in the Cardiac Laboratory diagnosed as having left bundle branch block during the period of this study were included except 43 patients with incomplete clinical data and 2 patients whose hospital records were lost. A follow-up study was made in all patients and dated from the time of the

From the Cardiac Laboratory, Massachusetts General Hospital, Boston, Mass.
Received for publication Sept. 1, 1950.
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***Ella Lyman Cabot Fellow.

TABLE I. AGE AND SEX DISTRIBUTION OF PATIENTS WITH LEFT BUNDLE BRANCH BLOCK WITH YEAR OF FOLLOW-UP, IF PATIENT IS ALIVE, OR YEAR DIED OR LOST FROM SERIES

AGE DISTRIBUTION	PRESENT STATUS	YEAR OF FOLLOW-UP 1	2	3	4	5	6	7	8	9	10	11	12	13	18	24	TOTALS		MALE	FEMALE
0 to 9.9	Alive	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	1			
	Dead	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	1	1	0
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0			
10 to 19.9	Alive	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0			
	Dead	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	1	0	1
	Lost	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	1			
20 to 29.9	Alive	—	—	—	—	—	2	—	—	—	—	—	—	—	—	—	2			
	Dead	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	3	3	0
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1			
30 to 39.9	Alive	1	—	—	1	1	1	—	1	—	—	—	1	—	—	—	6			
	Dead	5	—	1	2	—	—	—	—	—	—	—	—	—	—	1	9	15	10	5
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0			
40 to 49.9	Alive	1	6	1	1	1	4	—	2	1	1	2	1	1	1	—	23			
	Dead	7	6	2	2	1	—	2	1	—	—	—	—	—	—	—	21	46	22	24
	Lost	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	2			
50 to 59.9	Alive	1	5	5	4	2	3	—	3	3	3	6	5	1	—	—	41			
	Dead	45	11	9	6	6	1	—	—	1	2	—	1	—	—	—	82	132	78	54
	Lost	6	—	—	2	—	1	—	—	—	—	—	—	—	—	—	9			
60 to 69.9	Alive	8	11	9	4	6	3	6	2	4	2	4	1	—	—	—	60			
	Dead	50	22	13	14	3	12	1	2	—	4	—	—	—	—	—	121	196	123	73
	Lost	6	2	2	1	1	1	—	1	—	1	—	—	—	—	—	15			
70 to 79.9	Alive	1	7	5	1	2	4	3	2	—	1	—	—	—	—	—	26			
	Dead	52	16	9	3	9	3	—	2	2	1	—	—	—	—	—	97	128	73	55
	Lost	4	1	—	—	—	—	—	—	—	—	—	—	—	—	—	5			
80 to 89.9	Alive	—	1	1	1	—	—	1	—	—	—	—	—	—	—	—	4			
	Dead	10	6	3	3	—	3	—	1	—	—	—	—	—	—	—	26	31	23	8
	Lost	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	1			
90 to 99.9	Alive	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0			
	Dead	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	2	2	2	0
	Lost	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0			
Totals																		555	335	220

first electrocardiographic diagnosis of left bundle branch block. The procedure was similar to that used in the study of right bundle branch block.

The study of these 555 patients is complete except for 34 patients who have been lost. (Seventeen were lost during the first year after the diagnosis was made, and 17 were lost at varying periods from 2 to 10 years later.) This group of 34 patients represents only 6 per cent of the total; therefore, the end results are not distorted. Information regarding the present status of the 163 patients still alive was obtained after January, 1949.

RESULTS

Table I shows the ages of the patients in decades with their status (alive, dead, or lost) in the year they were last followed and the number of male and female patients in each decade. The age was that of the patient's previous birthday. A total of 535, or 96 per cent of the entire series, were over the age of 40 years, and a total of 335, or 60 per cent of the series, were males. The highest incidence of left bundle branch block occurred during the seventh decade, comprising a total of 196, or 35 per cent of the entire series.

TABLE II. DISTRIBUTION OF PATIENTS ALIVE, DEAD, AND LOST IN EACH YEAR OF FOLLOW-UP

YEAR OF FOLLOW-UP	PATIENTS STILL ALIVE	PATIENTS DEAD	PATIENTS LOST	TOTAL
1	12	170	17	199
2	30	62	6	98
3	21	37	2	60
4	12	30	3	45
5	12	19	1	32
Total of patients followed less than 6 years	87	318	29	434
6	17	19	2	38
7	10	3	0	13
8	10	6	2	18
9	8	3	0	11
10	7	7	1	15
11	13	0	0	13
12	8	1	0	9
13	2	0	0	2
18	1	0	0	1
24	0	1	0	1
Total of patients followed 6 years or more	76	40	5	121
Grand total	163	358	34	555

In Table II the patients are tabulated according to the number of years followed and their status at the time of completion of their follow-up, as either alive (during the year 1949), dead, or lost. In the latter 2 instances they are listed according to the year of follow-up in which they died or were lost. All patients followed less than 1 year are listed in the first year group. Those fol-

lowed more than 1 year, but less than 2, are listed in the second year group, and so forth.

A total of 199 patients, or 36 per cent of the entire series, was followed less than 1 year, and 170 of these patients, or 85 per cent, died during this period. The others were lost (9 per cent) or were still alive (6 per cent). The diagnosis of left bundle branch block was made in the latter patients during 1948.

Of the 358 deaths, there were 299, or 81 per cent, that occurred before the fifth year of follow-up. It will be noted that a total of 121 patients, representing 21 per cent of the entire series, is known to have lived longer than 5 years after the diagnosis of left bundle branch block was made; 76 were still alive, 40 were dead, and 5 patients were lost. Of the total 34 patients lost, 29 were lost before the sixth year.

Table III is an analysis of the survival periods arranged according to age in decades at the time of the diagnosis of left bundle branch block. The total group is compared with those who survived the first year of follow-up. The total series had a survival period to date of 3.3 years, and, as might be expected, there was a decrease in survival time from the younger to the older age groups. The 358 patients who survived the first year had an average survival time of 4.9 years.

TABLE III. AVERAGE SURVIVAL PERIODS IN RELATION TO PATIENTS' AGE WHEN LEFT BUNDLE BRANCH BLOCK WAS DIAGNOSED

AGE GROUP (YEARS)	TOTAL NO. PATIENTS IN SERIES	PATIENTS WHO WERE KNOWN TO HAVE SURVIVED 1 YEAR	AVERAGE SURVIVAL PERIOD (YEARS)	
			TOTAL PATIENTS IN SERIES	PATIENTS WHO SURVIVED 1 YEAR
0 to 9.9	1	1	11.0	11.0
10 to 19.9	1	1	8.0	8.0
20 to 29.9	3	3	4.7	4.7
30 to 39.9	15	9	4.8	7.7
40 to 49.9	46	37	4.5	5.5
50 to 59.9	132	80	3.6	5.7
60 to 69.9	196	133	3.3	4.6
70 to 79.9	128	72	2.4	4.1
80 to 89.9	31	21	2.6	3.7
90 to 99.9	2	1	1.0	2.0
Total	555	358	3.3	4.9

In the first section of Table IV, the survival periods were calculated separately for the sexes. The females had a survival period of 3.8 years. Of the 220 females there were 81 still alive (37 per cent). The survival period of the males, 2.9 years, averaged almost 1 year less than that of the females, and only 24 per cent (82 patients) were still alive. Seventy per cent of the females survived 1 year as compared to 60 per cent of the males.

The patients were next separated (Table IV) into those with an inverted T wave and those with a flat or upright T wave in Lead I (typical and atypical bundle branch block) of the first electrocardiogram demonstrating left bundle

branch block. There was a slightly longer survival period for those with an upright or flat T in Lead I than there was for those having an inverted T in Lead I, or 3.8 years as compared with 3.1 years. In those who survived the first year, the survival periods were 5.5 and 4.6 years, respectively. Sixty-seven per cent of the atypical and 63 per cent of the typical group survived the first year.

TABLE IV. THE RELATIONSHIP OF SEX, DIRECTION OF T_1, PRESENCE OF Q_1, AND HEART SIZE TO SURVIVAL PERIOD IN LEFT BUNDLE BRANCH BLOCK

	TOTAL PATIENTS		PATIENTS WHO SURVIVED 1 YEAR		AVERAGE SURVIVAL PERIOD (YEARS)	
	NO.	%	NO.	%	OF TOTAL PATIENTS IN SERIES	OF PATIENTS WHO SURVIVED 1 YEAR
1. Sex						
Male	335	60	201	60	2.9	4.6
Female	220	40	155	70	3.8	5.3
2. Direction of T_1						
Typical left bundle branch block (inverted T_1)	381	69	240	63	3.1	4.6
Atypical left bundle branch block (upright T_1)	174	31	116	67	3.8	5.5
3. Presence of Q_1						
Q wave present in Lead I	103	19	59	57	2.9	4.8
Q wave absent in Lead I	452	81	297	66	3.3	4.9
4. Heart Size						
No cardiac enlargement	113	20	81	72	4.3	5.8
Slight cardiac enlargement	155	28	99	64	3.5	5.3
Moderate cardiac enlargement	180	33	113	63	2.9	4.4
Marked cardiac enlargement	107	19	63	59	2.5	4.0
Total	555	100	356	64	3.3	4.9

In the third section of Table IV, the patients were classified with regard to the presence or absence of a Q wave in Lead I. A total of 103 patients (19 per cent of the series) had such a Q wave. There were only 6 patients who had a Q wave deeper than 2 mm. In 25 patients it was 0.5 mm., in 51 patients it was 1.0 mm., and in 21 patients it was 2.0 mm. This finding seems to have had little effect on survival time.

The last portion of Table IV is the most significant. Here the patients were arranged according to the size of their hearts at the time left bundle branch block was diagnosed. It is apparent that a definite relationship between the size of the heart and survival time exists. The 113 patients with no apparent heart enlargement had an average survival time of 4.3 years, and 72 per cent survived

the first year with an average survival time of 5.8 years. In contrast, the 107 patients with marked enlargement of the heart had an average survival time of 2.5 years, and the 63 patients who survived the first year had a survival time of 4.0 years. Those with slight or moderate enlargement of the heart were between these extremes. In other words, those patients with hearts of normal size had approximately 1 year longer survival time than the average patient, while those with marked enlargement of the heart had about 1 year shorter survival period. There were 44 per cent of the patients with normal size hearts still alive, while only 19 per cent of those with markedly enlarged hearts survived.

TABLE V. AVERAGE SURVIVAL PERIODS OF PATIENTS WITH LEFT BUNDLE BRANCH BLOCK ARRANGED ACCORDING TO DURATION OF THE QRS COMPLEX

QRS DURATION (SECONDS)	TOTAL PATIENTS	PATIENTS SURVIVING 1 YEAR	SURVIVAL PERIOD (YEARS)	
			OF ENTIRE GROUP	OF PATIENTS SURVIVING 1 YEAR
0.12	148	90	2.9	4.5
0.13	129	85	3.8	5.5
0.14	83	54	3.5	5.2
0.15	85	58	3.8	5.3
0.16	67	44	2.7	3.9
0.17	13	8	3.3	5.3
0.18	19	12	2.0	3.0
0.19	5	2	2.5	6.0
0.20	6	3	2.0	3.7
Total	555	356	3.3	4.9

Table V gives the number of patients and their survival periods arranged in groups according to the duration of the QRS complex in the standard leads. The largest number of patients occurred in the group with QRS complexes of 0.12 second (148). Those with the longer QRS complexes such as 0.17 to 0.20 second had a shorter survival time (2.4 years) compared with those with a QRS duration of 0.13 to 0.15 second (3.7 years). The percentage of patients surviving 1 year was likewise less in the higher ranges. Only 58 per cent of the patients with a QRS duration of 0.16 to 0.20 second survived the first year, while 66 per cent of those with QRS duration of 0.13 to 0.15 second survived the first year. An exception was the group with QRS complexes of 0.12 second duration with only 61 per cent surviving the first year. The survival time for this group (2.9 years) and for those who survived 1 year (4.5 years) was lower than in any other group with a QRS duration of less than 0.16 second.

Table VI shows the relationship between the duration of the QRS interval and the heart size as determined by roentgenogram. In general, where the groups were large enough to indicate a trend, the percentage of patients with marked cardiac enlargement increased as the QRS interval increased. This indicates that the longer QRS intervals were generally associated with a more severe type of heart disease. The higher mortality in the group with QRS intervals of

0.12 second was not primarily related to long-standing heart disease with cardiac enlargement, since there were fewer patients in this group with marked cardiac enlargement than in several of the groups with a longer average survival time, nor did it seem to be related to a greater incidence of heart failure. In the entire series 52 per cent of the patients had no evidence of left or right ventricular failure at the time of the diagnosis of left bundle branch block. In the group of 148 patients with a QRS duration of 0.12 second, there were 57 per cent without heart failure. There were 22 per cent with left ventricular failure and 26 per cent with combined left and right ventricular failure in the entire series, compared to 19 per cent and 24 per cent, respectively, for the group with a QRS duration of 0.12 second. The incidence of clinical coronary artery insufficiency in the entire series was 38 per cent, and in the smaller group it was 39 per cent. Hypertension was present in 62 per cent of the entire series and in 52 per cent of the smaller group. If the survival times were calculated separately for the sexes, those for the 92 males with a QRS duration of 0.12 second were 2.1 years for the total group and 3.6 years for those who survived the first year. The 56 females had survival times of 4.1 and 5.5 years, respectively. The lower survival time for the group with QRS duration of 0.12 second was due, therefore, to the short survival time of the males in this group.

TABLE VI. PATIENTS WITH LEFT BUNDLE BRANCH BLOCK
ARRANGED IN ORDER OF THE DURATION OF THE QRS INTERVAL AND THE SIZE OF THE HEART

QRS DURATION (SECONDS)	SIZE OF THE HEART								TOTAL PATIENTS	
	NORMAL		SLIGHTLY ENLARGED		MODERATELY ENLARGED		MARKEDLY ENLARGED			
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
0.12	33	22	41	28	51	34	23	16	148	100
0.13	29	23	40	31	39	30	21	16	129	100
0.14	21	25	23	28	25	30	14	17	83	100
0.15	19	22	27	32	23	27	16	19	85	100
0.16	9	14	14	21	29	43	15	22	67	100
0.17	1	8	3	23	6	46	3	23	13	100
0.18	0		5	26	4	21	10	53	19	100
0.19	0		1	20	1	20	3	60	5	100
0.20	1	17	1	17	2	33	2	33	6	100
Totals	113	20	155	28	180	33	107	19	555	100

There were 66 deaths in this group of 92 males, and 55, or 83 per cent, occurred before the fourth year. This was a higher proportion than in the group of males with a QRS duration of 0.13 second (68 per cent) or in the entire series (75 per cent). The survival time for the 66 males who died was 1.8 years, and for the 55 who died before the fourth year, it was 1.0 year. Of these 55 patients there were 24 with and 31 without the clinical manifestations of coronary artery insufficiency at the time of the diagnosis of left bundle branch block. The survival time of the former group was 1.2 years and of the latter group 0.9 year.

Since these 55 patients were the principal reason for the shortened survival time of the group with a QRS duration of 0.12 second, the causes of their deaths are of interest. The deaths of the 24 with clinically manifested coronary artery insufficiency were due to acute myocardial infarction in 17 patients, congestive heart failure in 6, and cerebral hemorrhage in 1. The deaths of the 31 patients without clinically manifested coronary artery insufficiency were due to acute myocardial infarction in 5 patients, congestive heart failure in 8, recurrence of rheumatic activity in 3, syphilitic aortitis in 1, cerebral hemorrhage in 1, postoperative pulmonary embolism in 3, mesenteric thrombosis in 1, and causes unrelated to the cardiovascular system in 9. The solution of this problem (the shorter survival time of males with left bundle branch block whose QRS duration is 0.12 second in duration) is, therefore, not complete. Undoubtedly, hidden, as well as clinically manifest, rapidly progressive coronary artery disease is an important factor.

In Table VII, the patients were classified according to their principal underlying disease. There were 6 main categories. The majority of the patients had hypertension or coronary artery disease; a few had rheumatic or syphilitic heart disease. The group with hypertension was subclassified to indicate whether or not there was also present angina pectoris, myocardial infarction, or rheumatic heart disease. Coronary artery disease was used to designate the presence of angina of effort, myocardial infarction (recent or old), or both. In the group designated as of miscellaneous etiology, cardiovascular conditions with only a few patients each were included, as well as certain systemic diseases which may or may not have an etiological relation to left bundle branch block. These systemic conditions were listed as the patient's principal illness when there was no other etiological cardiac diagnosis made. The final group was designated as of undetermined etiology, and here were included patients with neither a clear-cut etiological cardiac diagnosis nor any important systemic disease.

Of the 71 patients in the final group, 64, or 90 per cent of the group, were over the age of 50 years. This was comparable to the entire series of 555 patients where there were 489 patients, or 88 per cent, over the age of 50 years. The proportion of males was slightly higher (65 per cent) in this group than in the whole series (60 per cent). It is interesting to note that almost exactly the same proportion of patients in this series were either dead or lost as in the total series (70 per cent and 71 per cent, respectively). These similarities suggest that the underlying heart disease was similar in the 2 groups. However, there was a greater proportion of normal size (38 per cent) and slightly enlarged hearts (34 per cent) in this group than in the entire series (20 and 28 per cent, respectively), and only 28 per cent of the hearts in this group were moderately or markedly enlarged in comparison to 52 per cent in the entire series. This suggests that the heart disease, whatever it was, had a less serious effect upon the patient's heart than it did in those with clinically recognized disease. In fact, in this series of 71 patients, there were 51 patients (71 per cent) who were without cardiac symptoms, the left bundle branch block often being found during a routine examination.

TABLE VII. ETIOLOGICAL CLASSIFICATION OF 555 PATIENTS WITH LEFT BUNDLE BRANCH BLOCK

CLINICAL DIAGNOSIS	MALE	FEMALE	TOTAL
Hypertension Group			
Hypertension alone	118	90	208
Hypertension and angina or myocardial infarct or both	59	58	117
Hypertension and rheumatic heart disease and angina	4	1	5
Hypertension and rheumatic heart disease	3	9	12
Total			342
Coronary Artery Disease Group (Without Hypertension)			
Angina pectoris	16	2	18
Myocardial infarction	29	6	35
Angina and myocardial infarct	16	8	24
Total			77
Rheumatic Heart Disease Group			
Rheumatic heart disease alone	11	10	21
Rheumatic heart disease and angina pectoris	7	1	8
Rheumatic heart disease and myocardial infarct	2		2
Total			31
Syphilitic Heart Disease	8	2	10
Total			10
Miscellaneous Etiologies			
Cor pulmonale	8	2	10
Rheumatoid arthritis	1	3	4
Myxedema	1	2	3
Congenital heart malformation	2		2
Diphtheritic myocarditis	1		1
Virus myocarditis	1		1
Scleroderma heart disease		1	1
Chronic constrictive pericarditis	1		1
Myotonia atrophica	1		1
Total			24
Undetermined Etiology	46	25	71
Total			71

At the completion of this study there were 21 of these 71 patients with heart disease of undetermined etiology still alive; 15 of these had no cardiac symptoms, while 6 manifested diminished cardiac reserve. Forty-one patients were dead; 10 died of noncardiovascular causes, while 31 died as a result of cardiovascular disease. Five patients were autopsied; 3 showed severe coronary artery disease (1 with myocardial infarction), 1 had calcification of the mitral ring which probably involved the left bundle branch, and the fifth patient died as a result of pulmonary infarction. Nine patients were lost at various intervals from the series.

Table VIII gives the number of patients and average survival times for the various etiological groups by sexes, individually and combined, for both the total groups and those who survived the first year. The entire series of 555 patients

TABLE VIII. AVERAGE SURVIVAL PERIODS IN YEARS OF 555 PATIENTS WITH LEFT BUNDLE BRANCH BLOCK IN RELATION TO ETIOLOGICAL FACTORS

ETIOLOGICAL FACTORS	NO. PATIENTS AND AVERAGE SURVIVAL PERIODS (YEARS)											
	TOTAL PATIENTS						PATIENTS WHO SURVIVED 1 YEAR					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
	NO.	SURVIVAL TIME	NO.	SURVIVAL TIME	NO.	SURVIVAL TIME	NO.	SURVIVAL TIME	NO.	SURVIVAL TIME	NO.	SURVIVAL TIME
Hypertension Group												
Entire hypertension group (with and without coronary artery disease or rheumatic heart disease)	184	3.1	158	3.8	342	3.4	118	4.6	112	5.2	230	4.9
Hypertension alone	118	2.9	90	4.0	208	3.4	71	4.5	67	5.3	138	4.9
Hypertension with coronary artery disease	59	3.4	58	3.5	117	3.5	44	4.5	39	5.0	83	4.7
Hypertension and angina	25	3.3	36	4.1	61	3.8	19	4.1	24	5.9	43	5.1
Hypertension and myocardial infarction	17	2.3	11	2.0	28	2.2	10	3.7	8	2.8	18	3.3
Hypertension and angina and myocardial infarction	17	4.8	11	3.0	28	4.1	15	5.4	7	4.3	22	5.0
Hypertension and rheumatic heart disease and angina	4	1.4	1	9.0	5	2.9	1	3.0	1	9.0	2	6.0
Hypertension and rheumatic heart disease	3	9.1	9	2.6	12	4.2	2	13.5	5	4.4	7	7.0
Coronary Artery Disease Group												
Entire coronary artery disease group (with and without hypertension or rheumatic heart disease)	133	2.9	76	3.3	209	3.0	82	4.5	47	5.0	129	4.7
Angina pectoris	16	3.8	2	4.0	18	3.8	9	6.4	2	4.0	11	5.8
Myocardial infarction	29	2.4	6	3.7	35	2.6	15	4.4	3	7.3	18	4.9
Angina and myocardial infarction	16	2.3	8	0.4	24	1.7	9	3.9	1	2.0	10	3.7
Remaining Etiologic Groups												
Entire remaining groups	81	2.9	45	4.6	126	3.5	46	4.9	36	5.7	82	5.3
Syphilitic heart disease	8	2.7	2	1.0	10	2.3	3	6.7	1	2.0	4	5.5
Rheumatic heart disease alone	11	2.0	10	5.8	21	3.8	4	4.8	7	8.3	11	7.0
Rheumatic heart disease and angina or myocardial infarction	9	1.3	1	2.0	10	1.4	4	2.3	1	2.0	5	2.2
Miscellaneous etiologies	16	3.6	8	4.0	24	3.7	12	4.6	6	5.3	18	4.8
Undetermined etiology group	46	3.0	25	4.6	71	3.6	27	4.9	22	5.2	49	5.0

had an average survival time of 3.3 years, and this increased to 4.9 years for those who survived the first year.

The 2 largest groups of patients were: first, the entire hypertension group (with and without coronary or rheumatic heart disease), which numbered 342 patients and had a survival time of 3.4 years (230 of these patients survived the first year with an average survival time of 4.9 years); and second, the entire coronary heart disease group which numbered 209 patients and had an average survival time of 3.0 years. (The 129 patients who survived the first year had a survival time of 4.7 years.) This decrease in survival time for the entire group was due mainly to the low survival time of males with myocardial infarction (with or without hypertension, rheumatic heart disease, or angina pectoris) and partly to the short survival time of females with myocardial infarction and hypertension or with myocardial infarction and angina pectoris. It is significant that the survival time of the coronary heart disease group was practically average in those who survived the first year. It is unusual that the group of patients with hypertension and coronary heart disease combined had as long a survival time (3.5 and 4.7 years) as the group with hypertension alone (3.4 and 4.9 years). This is even more unusual when only the males are considered. The 118 males with hypertension alone had an average survival time of 2.9 years, while the 59 males with hypertension plus coronary heart disease had an average survival time of 3.4 years. It is interesting to note that both sexes with either angina pectoris alone or hypertension and angina pectoris had slightly better survival times than the patients of the entire series and even than those with hypertension alone. It is probable that many of the patients diagnosed as having hypertension alone had undiagnosed coronary heart disease of an important degree, as has been demonstrated frequently by post-mortem examination; it is likely that such patients die sooner, but of that we do not have definite evidence in the present study.

In this series there have been 357 deaths to date with 71 post-mortem examinations. In Table IX the diagnoses of all the deaths have been listed separately for those with and without autopsy confirmation. Approximately 50 per cent of both groups died of either congestive heart failure or myocardial infarction. Pulmonary embolism accounted for 13 per cent of the deaths in the autopsy group; 8 of the 9 deaths occurred postoperatively. Only 10 per cent of the deaths in both groups were not related to the cardiovascular-renal system. This was in marked contrast to the follow-up study of the 163 living patients. In this latter group 84, or approximately 52 per cent, were without any disability and had not had a single symptom of significance related to the cardiovascular system at the time of their final follow-up. There were 34 patients (21 per cent of the living group) with mild cardiovascular disability, 36 (22 per cent) with moderate disability, and only 9 (5 per cent) with marked disability.

In comparing the weights of the hearts of 67 autopsied patients with the QRS duration of their electrocardiograms, only a slight correlation was found. There were 41 hearts weighing under 600 grams, and of these 51 per cent had a QRS duration of 0.12 or 0.13 second. Of the 26 hearts weighing over 600 grams,

54 per cent (14) had a QRS duration of 0.14 second or greater. This poor correlation was in contrast to the better correlation found in Table VI, where the heart size (which included dilatation), usually determined by x-ray examination, was correlated with the QRS duration. The cause of prolonged conduction time through one of the ventricles may be due, in some cases, to the increased bulk of that ventricle. This is suggested by the variation of the normal QRS duration from 0.05 second in the human infant to 0.10 second in the human adult and to 0.20 second in the adult elephant.[28] In other cases it is due to an abnormal course of the excitation wave. Two examples of the former may be cited. The 2 largest hearts in the autopsy series weighed 1,080 and 1,100 grams, and both had a QRS duration at the time of their electrocardiographic examination of only 0.12 second. The former was a man, 69 years old, with angina pectoris and a history of 2 previous infarctions of the myocardium (6 and 7 years prior to death) and death from his third infarct. His heart had been huge for 3 years. The second patient was a physician who died at the age of 41 years of an acute recrudescence of rheumatic fever and acute glomerulonephritis. He showed at autopsy chronic rheumatic involvement of both the mital and aortic valves with coronary artery disease.

TABLE IX. ANALYSIS OF 357 DEATHS OCCURRING IN A SERIES OF 555 PATIENTS WITH LEFT BUNDLE BRANCH BLOCK

CAUSE OF DEATH	DEATHS WITHOUT AUTOPSY CONFIRMATION		DEATHS WITH AUTOPSY CONFIRMATION	
	NO.	%	NO.	%
Congestive heart failure in patients with hypertension or coronary artery disease	73	26	17	24
Myocardial infarction	73	26	18	25
Sudden death	47	16	2*	
Rheumatic heart disease	9	3	5	7
Syphilitic heart disease	6	2	3	4
Chronic cor pulmonale	1	0.5		
Scleroderma heart disease			1	2
Stokes-Adams attack	2	1		
Cerebral accident (hemorrhage, thrombosis, embolism)	23	8	8	11
Uremia	8	3	3	4
Arteriosclerosis and senility	8	3		
Pulmonary embolism	6	2	9	13
Miscellaneous (noncardiovascular-renal in origin)	30	10	7	10
Totals	286	100	71	100

*Autopsy revealed rheumatic valvular disease, 1 with aortic insufficiency and 1 with aortic stenosis and mitral stenosis; they are included under rheumatic heart disease.

SUMMARY AND CONCLUSIONS

1. A consecutive series of 555 patients, diagnosed as having left bundle branch block in the Cardiac Laboratory of the Massachusetts General Hospital

during the years 1937 to 1948, has been analyzed to determine the factors influencing their survival periods. The average survival period to date for the group was 3.3 years (163 still alive), and for those who survived the first year, it was 4.9 years (151 still alive).

2. In this study there were 335 males and 220 females. Almost 90 per cent of the patients were over 50 years of age. The highest incidence occurred in the seventh decade and included 35 per cent of the patients. There were 199 patients followed less than 1 year, and of these 170 were dead, 12 were still alive, and 17 were lost during the follow-up period. Of the 356 patients followed longer than 1 year, 151 were still alive, 188 were dead, and 17 were lost. There were 121 patients (21 per cent of the series) followed 6 years or longer; 76 were still alive, 40 were dead, and 5 were lost. One patient was still alive 18 years after the diagnosis of left bundle branch block, 2 patients were still alive after 13 years, and 1 patient was known to have lived for 24 years before his death.

3. Survival periods were longer in the younger than in the older patients.

4. Females with left bundle branch block had a longer survival time than males (3.8 against 2.9 years).

5. The survival period for patients with a Q wave in Lead I was 2.9 years while those without such a finding survived 3.3 years. In general, the patients with the longest QRS duration had the shortest survival periods. An important and single exception to this rule was the group with the shortest QRS duration (0.12 second) that had a survival period of only 2.9 years; this was less than the survival period of all the other groups with a QRS duration less than 0.16 second. A possible explanation is that this group included several males with rapidly progressive coronary artery disease terminating fatally within 3 years of the discovery of left bundle branch block.

6. A slight but direct correlation was found between heart size and QRS duration. About one-fifth of the patients with a QRS duration under 0.16 second had normal size hearts in contrast to only an occasional patient (5 per cent) with a QRS greater than this. Almost one-half of the patients with a QRS duration greater than 0.16 second manifested marked cardiac enlargement, while, in contrast, less than one-fifth of the patients who had a QRS duration of less than 0.16 second showed this finding. In a smaller group of 67 patients who died and were examined post mortem, no clear correlation was found between the QRS duration during life and the weight of the heart; however, this did not take into account dilatation of the heart which was often of considerable degree.

7. Heart size was definitely related to survival time. Patients with no cardiac enlargement survived 4.3 years, while those with greatly enlarged hearts survived only 2.5 years. Furthermore, 44 per cent of the patients who had normal size hearts at the time of diagnosis of left bundle branch block were living, while only 21 per cent of those with moderate and marked cardiac enlargement were still alive.

8. The commonest etiological relationship with left bundle branch block in this series was hypertension with 342 patients so diagnosed; in addition, 122 of these had clinical manifestations of coronary heart disease (angina pectoris

and/or myocardial infarction). A total of 209 patients had coronary heart disease. A total of 429 patients (77 per cent of the series) manifested either hypertension or coronary heart disease or both. There were 48 patients with rheumatic heart disease, 10 with syphilitic heart disease, and 10 with cor pulmonale (probably accompanied by "silent" coronary heart disease). Other diagnoses included congenital cardiovascular malformations (2), virus myocarditis (1), and diphtheritic myocarditis (1). A few patients had no obvious etiological cardiac diagnosis but presented a serious systemic disease such as rheumatoid arthritis (4), myxedema (3), and myotonia atrophica (1).

There were 71 patients without an obvious etiological cardiac diagnosis and without an important systemic disease. After varying periods of follow-up, we have autopsy evidence of the cause of the heart disease in 5 of these; there were 3 with severe coronary artery disease (one with myocardial infarction), 1 with calcification of the mitral ring, and 1 with idiopathic right ventricular hypertrophy (plus slight left ventricular hypertrophy). Of the living patients, 1 later developed hypertension, and another developed angina of effort.

9. The relationship of the underlying heart disease to the survival time showed the poorest prognosis in those with coronary artery disease (3.0 years compared to 3.3 years for the entire series). The hypertension group as a whole had a survival time of 3.4 years. The undetermined etiology group had an average survival period of 3.6 years. These figures showed less variation than might be expected to occur with different etiological types of heart disease. Some of the smaller subgroups (for example, those with hypertension, angina, and myocardial infarction) which showed a better than average survival time indicated that the degree of cardiac impairment imposed by the underlying heart disease was more important than the cause of the lesion.

10. Of the total 357 deaths, 255, or 71 per cent, were due directly to heart disease, with the majority having either congestive heart failure or myocardial infarction. There were 31 deaths (9 per cent) due to cerebrovascular accident, and only 37 deaths (10 per cent) were unrelated to the cardiovascular-renal system.

ADDENDUM

Since submitting this paper for publication, the following article has come to our attention: Mezzasalma, G., and Moschini-Antinori, E.: Considerazioni cliniche ed elettrocardiografische su 50 casi di blocco di branca, Cuore e circolaz. **34**:88, 1950. The authors of this article stated that hypertension with an acute increase in the size of the heart, especially of the left ventricle, was found in the majority of the patients with left bundle branch block. This fact induced them to believe that the cause of the greatest part of the left bundle branch block was overwork and enlargement of the left ventricle which in some way afterwards caused a disturbance of the conduction system of the left branch. The relatively high percentage of patients in our study having a normal size heart (45 per cent with right and 20 per cent with left bundle branch block) indicates that this is not the only factor. The better correlation of QRS conduction with heart size, as measured by the roentgenogram, than with heart weight at autopsy does suggest the importance of dilatation; however, the evidence is not clear as to whether this is the cause of the conduction defect or whether both reflect progression of the underlying heart disease.

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PROGNOSIS IN BUNDLE BRANCH BLOCK

III. A Comparison of Right and Left Bundle Branch Block With a Note on the Relative Incidence of Each

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THE various factors influencing the survival time in right and left bundle branch block have been analyzed separately in the first 2 parts of this study. In the present paper these 2 types of conduction defects will be compared with regard to survival time and to their relative incidence.

Multiple precordial leads were not available in about one-third of the patients used in this study. In order to determine the error in classifying right and left bundle branch block from the standard limb leads, a group of tracings showing bundle branch block were interpreted and classified. The tracings were first classified as to the type of bundle branch block from the standard limb leads, and then compared with an interpretation based on the precordial leads. All cases of bundle branch block occurring in 10,000 consecutive electrocardiograms taken during a year and one-half period between 1947 and 1949 were used. The criteria used for classification were those outlined in the 2 previous parts of this study.

Right bundle branch block occurred 76 times and was diagnosed correctly from the limb leads 73 times. In 1 instance left bundle branch block was diagnosed from the limb leads, while the precordial leads showed right bundle branch block, and in 2 instances the disturbance was not clear from the limb leads; however, the diagnosis could be made from the precordial leads. (The latter 2 patients would not have been used in this study if precordial leads were not available.)

Left bundle branch block occurred 83 times and was diagnosed correctly from the standard limb leads 82 times. In 1 instance right bundle branch block appeared to be present in the limb leads whereas left bundle branch block was shown to be present in the precordial leads.

We may conclude that the error in classifying right and left bundle branch block from the standard limb leads is small, less than 1.5 per cent; therefore, the use of the standard limb leads does not invalidate this study.

From the Cardiac Laboratory, Massachusetts General Hospital, Boston, Mass.
Received for publication Sept. 1, 1950.

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In the first 2 parts of this study, left bundle branch block was found to occur approximately twice as often as did right bundle branch block. The pattern of right bundle branch block occurred once in every 243 electrocardiograms and left bundle branch block once in every 123 electrocardiograms. In the 10,000 electrocardiograms analyzed, right bundle branch block occurred once in every 131 tracings and left branch block once in every 120 tracings. These figures suggest that right bundle branch block is more common than earlier studies indicated, and future studies may show that there is no "common" or "uncommon" type of bundle branch block.

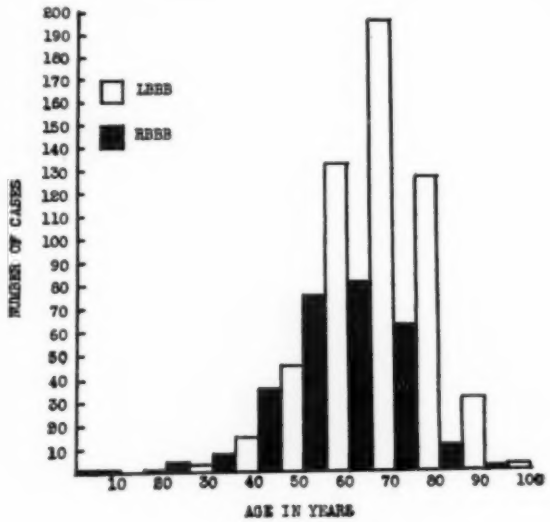

Fig. 1.

COMPARISON OF RIGHT AND LEFT BUNDLE BRANCH BLOCK

Fig. 1 is a frequency distribution curve of the patients with right and left bundle branch block in each age group. Both types of bundle branch block showed the greatest incidence between the ages of 60 and 70 years with 29 per cent of the right and 35 per cent of the left branch type occurring during this period. There was a striking similarity between the 2 curves except for the preponderance of patients in the group with left bundle branch block in the sixth decade.

Fig. 2 is a graph showing the average survival time for the 2 types of bundle branch block at various age levels. The total number of patients in both age groups is shown along with those who survived the first year of follow-up in each series. These curves illustrate several interesting phases. In patients under the age of 10 years, right bundle branch block appeared to show a longer survival time than did the left type of defect; however, the number of patients was too small to justify any conclusion. In patients between the ages of 30 and 40 years, left bundle branch block showed a longer average survival time than did the right type of conduction defect, both in the total number of patients

in the series and in those who survived the first year of follow-up. Between the ages of 40 and 50 years, patients with right bundle branch block showed a longer survival period than did those with left branch block; however, the difference was not great except in those who survived the first year of follow-up. In patients over the age of 50 years, there was only a slight difference in average survival times for the total group of patients with right and left bundle branch block. The patients with right bundle branch block showed only a very slightly greater survival time than did those with left bundle branch block between the ages of 50 and 80 years.

Sex.—Males predominated in both series with 72 per cent in the right and 60 per cent in the left bundle branch block group. Males predominated in all age groups except the group between the ages of 30 and 40 years with right and the group between 40 and 50 years with left bundle branch block, where there was a slight preponderance of females. In both series females tolerated the lesions better than did the males. It is doubtful that this represents anything more than the recognized fact that females tolerate coronary and hypertensive heart disease better than do males.

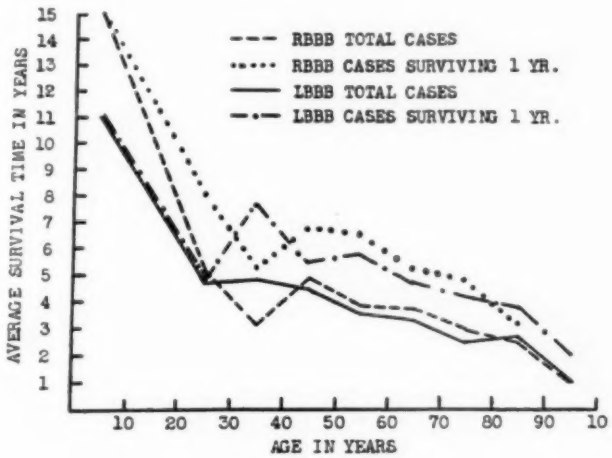

Fig. 2.

Electrocardiographic Data.—In right bundle branch block no significant difference was found in the average survival time of those showing typical and atypical curves. In left bundle branch block a slightly longer average survival time occurred in those showing atypical curves with a definite increase in this difference in the group who survived the first year of follow-up.

A Q wave was present in Lead I in 19 per cent of the patients with left bundle branch block. The average survival time of patients showing this finding was slightly less than those not showing it in the total group of patients; however, in those who survived the first year of follow-up, there was no significant difference in survival time. It appears that the presence of a Q in Lead I as an isolated finding is of only slight prognostic significance.

In both the right and left bundle branch block groups the average survival time was slightly less for patients with QRS durations of 0.12 second than for those with intermediate QRS intervals of 0.13 to 0.14 second. The reason for this was not clear except that these patients obviously had more severe heart disease since they did not survive long. It may well be that enlargement of the heart (a manifestion of severe heart disease) and/or diffuse myocardial damage as a result of more severe coronary disease caused the prolonged intraventricular conduction defect rather than a smaller local lesion interrupting the bundle branches. This finding may also explain the poorer prognosis of some of the earlier studies which included a preponderance of patients with QRS complexes of shorter duration.

Heart Size.—In most types of heart disease except that due to narrowing or obstruction of the coronary arteries, the heart size reflects the severity of the disease and, to some degree, the functional status of the patient. In both right and left bundle branch block the size of the heart showed a higher degree of correlation with survival time than any other single factor. Those patients with no cardiac enlargement showed longer survival periods than the average for their respective groups, and as the heart size increased, survival time decreased. This is the most significant positive finding in this study since it clearly indicates that survival time is more closely related to the cardiac status of the patient than to the electrocardiographic finding of bundle branch block.

Etiology of the Underlying Heart Disease.—It might be supposed that the etiological type of heart disease associated with bundle branch block would have a great effect on survival time; however, our results did not show this to be the case. The group with right bundle branch block in whom the etiology was not clear (including a miscellaneous group, many of whom had so-called "asymptomatic coronary" disease) showed the longest survival time both in the total patients and in those surviving the first year. Hypertensive patients had the next longest survival periods, and coronary heart disease patients followed these. Patients with rheumatic heart disease and right bundle branch block had the shortest survival period. There were too few patients in the other groups to be significant.

The patients with left bundle branch block and rheumatic heart disease tolerated the lesions quite well, even when coronary heart disease or hypertension was also present. There was very little difference between hypertensive and coronary heart disease, but the former showed a slightly longer survival time. Those patients in whom the etiology was uncertain did not show a significantly longer survival period than the total for the group.

SUMMARY AND CONCLUSIONS

The case records, including a follow-up study of 836 patients showing the electrocardiographic patterns of right or left bundle branch block, have been analyzed separately and compared. These patients were unselected except that those in whom the clinical data or hospital records were unavailable were not

used. The majority of the patients in this study were first seen between the years 1937 and 1948; however, some had been seen previous to 1937, and in those patients the survival time was taken from the earliest electrocardiogram showing bundle branch block.

1. The average survival time for the 281 patients with right bundle branch block was 3.9 years and for the 555 patients with left bundle branch block 3.3 years. The 185 patients with right bundle branch block who survived the first year of follow-up had an average survival time of 5.7 years, and the 356 patients with left bundle branch block who survived the first year had an average survival time of 4.9 years. From these figures it would appear that right bundle branch block shows a slightly better prognosis than left bundle branch block; however, an analysis of the survival time of different age groups indicates that in patients over the age of 50 years there is only slight difference between the average survival periods of right and left bundle branch block either in the total number of patients or in the group who survived the first year. Below the age of 50 years, right bundle branch block has the longer survival period except in patients between the ages of 30 and 40 years, and this occurs in spite of a high proportion of females to males in this age group. The explanation suggested for this is the high proportion of females with rheumatic heart disease in this group, the etiological type of heart disease with right bundle branch block showing the shortest survival period.

2. The high degree of correlation between heart size and survival time for both types of bundle branch block, we believe, indicates that the functional reserves of the individual patients provide the most important criteria upon which to base a prognosis. The degree of cardiac enlargement simply gives an objective measure of the strain placed on the cardiovascular system by the underlying lesion.

3. The fact that females tolerated the lesions better than did the males reflects the well-known fact that females tolerate hypertensive and coronary heart disease better than do males.

4. The difference in survival time between the several etiological types of heart disease and combinations thereof reflects the amount of cardiovascular strain from the underlying disease rather than a specific effect of the conduction defect. The low survival time of patients with rheumatic heart disease and right bundle branch block indicates the severity of the burden that must be placed on the heart in these patients before bundle branch block appears. By the same token, the patients with left bundle branch block, hypertension, angina pectoris, and myocardial infarction did better than average because the underlying disease, while serious, did not (in this particular group) put so serious a strain on the heart as did certain other lesions.

5. The electrocardiographic pattern of either right or left bundle branch block, while indicating heart disease, does not per se permit a prognosis. A long survival time free of symptoms is not incompatible with this electrocardiographic finding. A complete evaluation of the patient's cardiac status, his functional reserve, and, frequently, the progression of his disease over a period of time is necessary before the prognosis can be estimated. Our figures indicate a

more favorable outlook than that of earlier studies, probably because of the increasing frequency with which electrocardiograms are being taken on patients with minimal cardiac symptoms.

6. When electrocardiography is more widely and routinely carried out, right and left bundle branch block will probably be found to occur in more nearly the same proportion than they did in the past.

ADDENDUM

In a paper delivered before the British Cardiac Society, Moore (Moore, H.: A Personal Follow-Up in 111 Cases of Intraventricular Heart Block, Brit. Heart J. **12**:207, 1950) concluded, as we did, that the functional cardiac reserve is the most important factor determining the prognosis of a patient showing bundle branch block. The average survival time in the above study was much less than our more extensive series, probably because the patients were selected from a group with more pronounced symptoms of heart disease.

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THE VENTRICULAR COMPLEX IN ESOPHAGEAL ELECTROCARDIOGRAPHY

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SHORTLY after the introduction of electrocardiography into clinical use, Cremer, in 1906[1] recorded the first esophageal electrocardiogram in human beings, after passing a large silver electrode into the esophagus of a sword swallower. In animal experiments, the anoesophageal lead was used extensively, but it was not until 1924 that the first adequate esophageal records in human beings were published.[2]

Esophageal electrocardiography has been employed because of the contiguity of the esophagus to the various chambers of the heart.[3] The esophagus leaves the spine at the level of the fifth thoracic vertebra and then lies in direct posterior relationship to the left auricle for a distance of 5 to 6 cm. to a point 2 to 3 cm. above the diaphragm. The close proximity of the esophagus to the left atrium affords a readily available method for the recording of atrial complexes of higher amplitude than those seen in the limb leads. The presence of an intrinsic deflection in such leads permits a more accurate analysis of electrical activity in the atria. Esophageal electrocardiography as applied to the human being was, therefore, primarily employed for the analysis of atrial complexes and arrhythmias.[2,4,5]

Although the esophageal ventricular patterns were also described, emphasis upon the analysis of their configuration was stressed only when the problem of the diagnosis of infarction of the posterior wall of the left ventricle was recognized.[6-11] Increased interest in esophageal electrocardiography was aroused by the introduction of the Wilson unipolar electrode[12] which made possible the recording of potentials arising from a more localized area of the heart.

The criteria for the diagnosis of posterior myocardial infarction by electrocardiographic methods have varied considerably. Whereas multiple unipolar precordial leads have proved to be of much value in determining the presence of variously located anterior wall infarctions, less reliable means have been available to determine the presence of infarction of the posterior wall of the left ventricle. Several standards have been utilized as based upon the presence of a Q wave in Lead III,[13,14] but more recent investigators have indicated the higher reliability of Lead aV_F[11] with the abnormal Q wave defined as measuring

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Received for publication June 7, 1950.

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0.03 second or more from onset to nadir and more than 25 per cent of the amplitude of the R wave.[15]

Confirmation or exclusion of the diagnosis of posterior wall infarction has depended upon both autopsy correlation and esophageal studies.[11] The employment of esophageal leads in the study of infarction of the posterior wall is based upon the proximity of the left ventricle to electrodes introduced into the esophagus.[3,4] This method affords the closest anatomical approach to the study of potentials of the human left ventricle without resorting to more complex procedures such as intracardiac catheterization. By means of such investigation, it was hoped that evidence of damage localized to the infra-atrial area could be recorded. In such instances, the finding at the ventricular level of a Q wave exceeding 0.4 mv. is considered by some as diagnostic of posterior infarction, especially if it is relatively large in proportion to the R waves.[9]

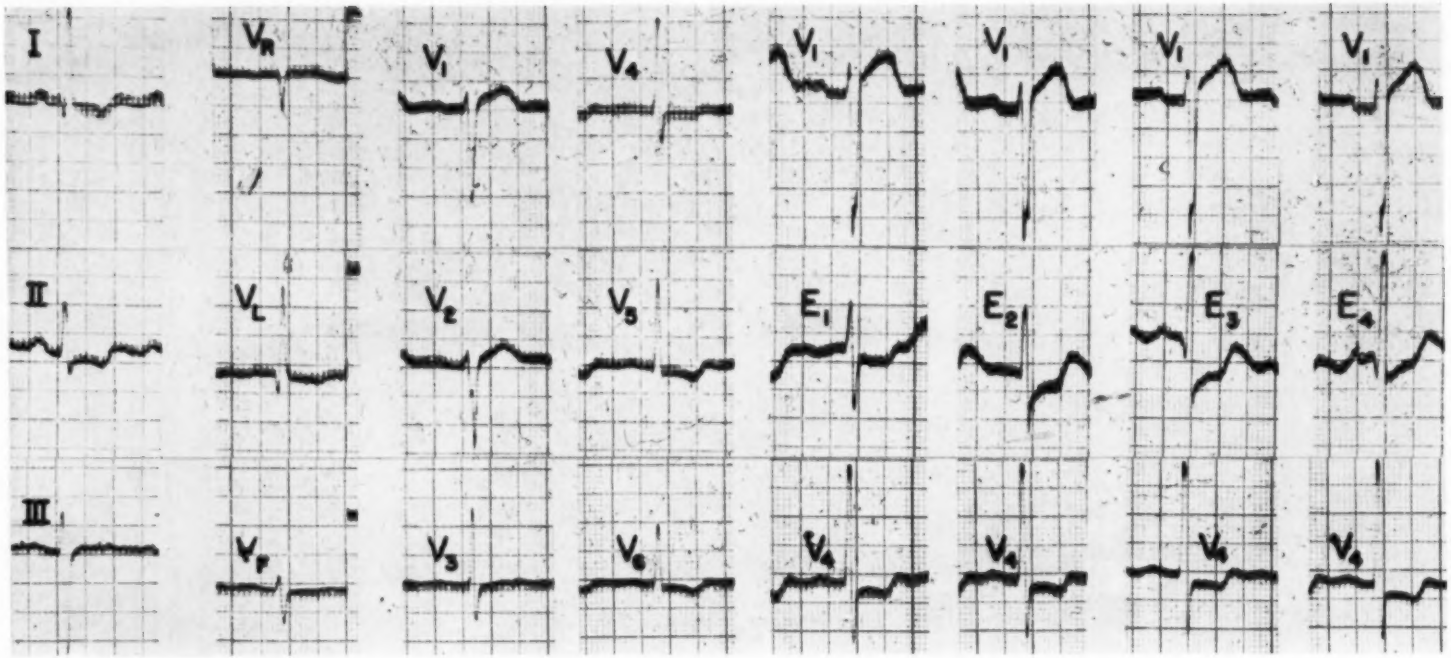
The significance of the presence of such Q waves as diagnostic of infarction has recently been questioned.[16,17] It is difficult to prescribe exact criteria for infarction until an analysis of the esophageal ventricular configuration has been made in normal and hypertrophied hearts. The following study was undertaken in an attempt to determine the esophageal pattern in various cardiac conditions.

METHODS

The group of individuals in this study comprised eighty-five persons and included patients with definite evidence in V_F of posterior myocardial infarction associated with a history and typical course of myocardial infarction due to coronary occlusion, individuals with borderline Q waves in V_F, and others without any history or evidence of infarction and with normal-sized hearts or various degrees of cardiac enlargement.

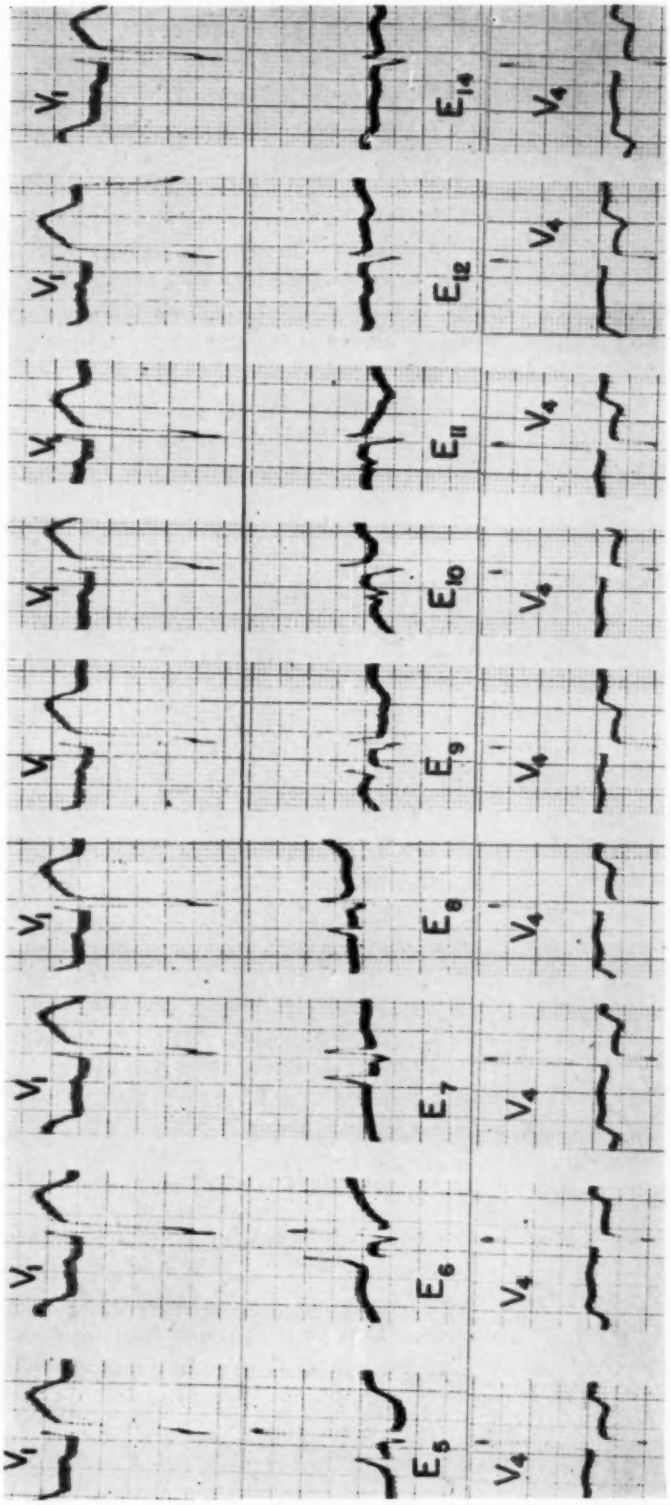
The esophageal electrode employed in this study consisted of a soft rubber tube with a central core of fifteen fine wires, each of which was separately connected to external metal bands placed 1.75 cm. apart. The tip of this tube was placed at least 6 cm. below the level of the diaphragm under fluoroscopic control and closely hugged the posterior and diaphragmatic contours of the heart. A regular sequence of esophageal electrocardiographic patterns was thus recorded from the diaphragmatic surface of the heart to supracardiac levels. The most distal electrode, E_1, thus reflects the potential at the diphragmatic surface of the heart, while E_{15} represents the most proximal electrode. The electrocardiograms were taken in the recumbent or semirecumbent position.

To minimize extraneous low-frequency potentials of gastric, esophageal, and diaphragmatic origin, an electric filter, as previously described,[18] was utilized. A Technicon Three-Channel Cardiograph was used, and records were frequently taken at double the normal speed to permit timing and evaluation of deflections in simultaneously recorded leads. Varying sensitivities were necessary to secure deflections of large amplitude, and the figures are labelled accordingly. With the aid of a Technicon external selector, it was possible to record simultaneous standard, esophageal, unipolar extremity, and precordial leads in any desired



A.

Fig. 1, *A* and *B*.—N. L., a 56-year-old white man, with angina pectoris for two years and hypertension. There was left ventricular hypertrophy on fluoroscopic examination. (1 mv. = 10 mm. in standard leads, 5 mm. in V_1 to V_6, 8 mm. in E_1 to E_6, and 12 mm. in E_7 to E_{14}.) E_1 at lower esophageal levels; E_{14} at supracardiac level. The P wave was upright in E_2; there was atrial intrinsic deflection in E_5; the P wave was inverted in E_{12}. The Q wave appears in E_3 and increases in depth at succeeding levels. Note the similarity of E_1 and V_F. (All records were taken simultaneously and have been remounted to conserve space.)



B.

(For legend see preceding page.)

combination. Lead V_F, as employed in this study, consisted of a Wilson unipolar extremity lead taken at 1.5 times the normal sensitivity.

Intracardiac electrocardiograms were recorded by right heart catheterization in several of the patients.

RESULTS

Multiple esophageal leads reveal a pattern of the diaphragmatic and posterior surfaces of the heart requiring careful analysis, which cannot be obtained by two or three records taken at widely separated intervals along the esophagus. In the present study, emphasis was placed upon the transition of esophageal patterns, and these are discussed under the headings of auricular deflections, ventricular deflections in normal-sized hearts, left ventricular hypertrophy, right ventricular hypertrophy, and posterior myocardial infarction. The significance of the RS-T segment deviations in these instances and in bundle branch block is being reported separately.[19]

Auricular Complexes.—In most cases there is a regular sequence in the transition of the auricular complexes. The esophageal leads reflecting the diaphragmatic surface of the heart reveal upright P waves (Figs. 1, *A* and *B*, and 2). At a slightly higher level, the downstroke becomes somewhat steeper in contour. Still higher, at atrial level, the amplitude of the P wave may be more than that of the ventricular complex because of the proximity of the electrode to the left atrium. The P wave at this level is diphasic (plus-minus) with a sharp downstroke characteristic of an intrinsic deflection. At supra-atrial levels, the amplitude decreases and the P wave becomes inverted.

The level of initial appearance of the atrial intrinsic deflection may, however, vary considerably with the position and the size of the heart. Lower esophageal levels may reveal an atrial intrinsic deflection, although ventricular surface potentials are still being recorded. Conversely, left ventricular cavity potential may be recorded prior to the appearance of the atrial intrinsic deflection.

Ventricular Pattern in Hearts of Normal Size Without Infarction.—The pattern obtained from the lower esophageal levels revealed the essential similarity of V_F to the leads obtained from the diaphragmatic surface of the heart. Although a variety of transitions were encountered, two of the most frequent will be discussed in detail; that is, those instances when E_1 and V_F were either qR or rS in configuration.

When the pattern was R or qR in configuration in the lower esophageal leads, the electrocardiogram which was recorded a few centimeters proximally revealed the appearance or increasing depth of the Q wave and the decreasing amplitude of the R wave (Fig. 2). Occasionally, qRs patterns were found localized to two or three esophageal levels. If the original pattern in the lower leads consisted of a small R wave followed by a deep S wave, a small Q wave made its appearance in the succeeding leads and gradually increased relatively in size as the R wave and S wave varied in amplitude.

In every instance, the Q wave increased in depth and duration until the complex was Qr or QS in configuration as higher levels were reached. Concurrently, the intrinsic atrial deflection gradually appeared, and the entire electrocardiogram represented the left ventricular cavity pattern, consisting of a large atrial wave with an intrinsic deflection and a ventricular complex of Qr or QS configuration. Supracardiac levels revealed a QS or Qr pattern preceded by an inverted P wave of low amplitude.

The level at which the ventricular cavity Q wave makes its initial appearance was found to vary somewhat according to the position of the heart (Figs. 3, 4, and 5). The simultaneous initial appearance of the cavity Q wave and the intrinsic atrial deflection was not a constant finding. In some instances the Q wave became equal to or larger than the R wave before the atrial intrinsic deflection was inscribed. Occasionally, the usual transition of a qR or rS pattern to the Qr or QS pattern, representing left ventricular cavity potential, may be interrupted by the recording of a QS pattern at isolated esophageal levels (Fig. 6).

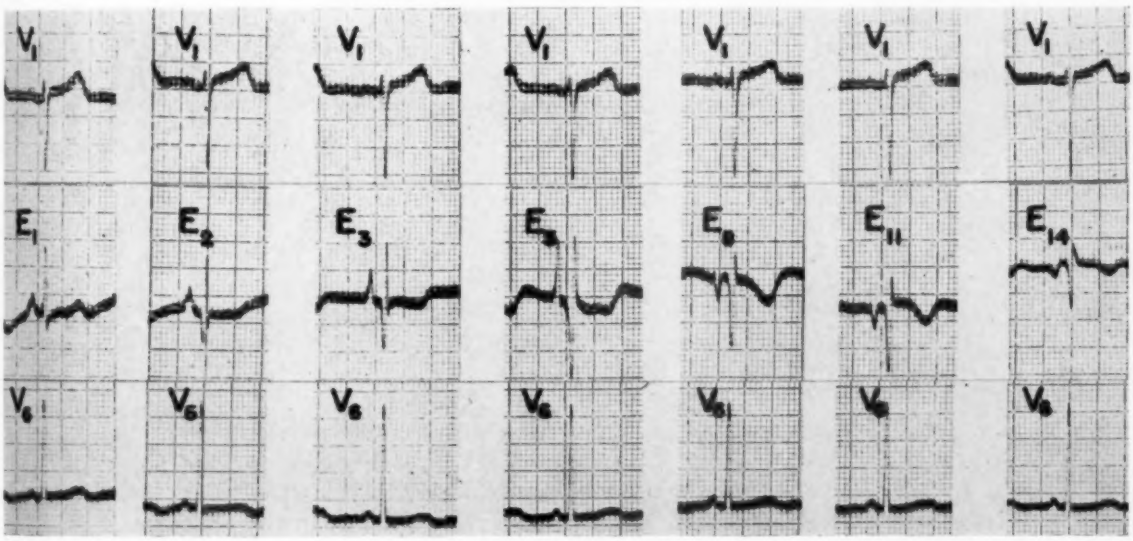


Fig. 2.—V. D., a 38-year-old white woman, with angina pectoris and hypertension. The heart was normal on examination. (1 mv. = 10 mm.) The P wave was upright in E_1; the atrial intrinsic deflection was best seen in E_5; the P wave was inverted in E_{14}. The Q wave appeared in E_2 and increased in depth at succeeding levels.

Thus, the lower esophageal electrodes record on the diaphragmatic surface of the heart the potentials of the chamber which can be either right or left ventricle. A transition zone is then reached for ventricular complexes as for atrial complexes, during which time the ventricular cavity Q wave makes its initial appearance and increases in amplitude. The ventricular complex becomes Qr or QS in configuration when the left ventricular cavity potential is tapped.

Left Ventricular Hypertrophy Without Infarction.—The twenty-two patients in this group were selected on the basis of typical electrocardiographic patterns of left ventricular hypertrophy and fluoroscopic evidence of enlargement of the

left ventricle. The lower esophageal pattern in one-third of these patients was qR or R in configuration and followed the transition of the ventricular complexes as observed in normal hearts. The lower esophageal pattern in the remaining two-thirds revealed an rS pattern with the S waves gradually diminishing in size a few leads proximally (Figs. 1,*A* and 1,*B*). As the higher levels were recorded, the R wave became of increased amplitude and a Q wave appeared which gradually increased relatively in depth until left ventricular cavity potential, as represented by a QS or Qr pattern, was obtained.

In three of these patients with marked cardiac enlargement, although an atrial intrinsic deflection was present for several levels, the ventricular pattern remained qR in configuration. At no level was a QS or Qr pattern recorded, and even at supracardiac levels, the pattern remained qR in configuration and resembled the left ventricular hypertrophy pattern as recorded in V_6 (Fig. 7).

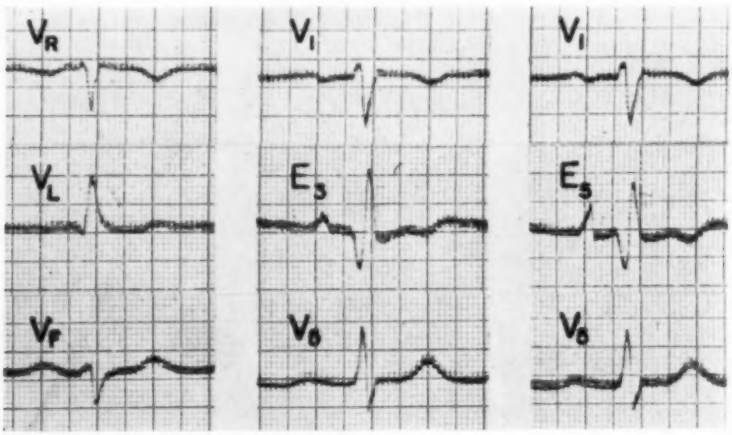


Fig. 3.—A. L., a 50-year-old white woman. (1 mv. = 10 mm.) There was an atrial intrinsic deflection in E_5 and a deep Q wave in E_2. (All records were taken at twice the normal speed.)

In five cases, although the usual transition in ventricular complexes occurred, a QR pattern was present at one to three levels earlier than the appearance of an atrial intrinsic deflection. In an additional two instances, the esophageal pattern appeared to be QR in configuration. However, comparison with a simultaneously recorded precordial lead revealed that a deflection, Q or R wave, inscribed in the precordial lead preceded the initial Q deflection in the esophageal lead by 0.03 second. In these two instances, the apparent QR of the esophageal lead was probably preceded by an isoelectric R wave.

In one patient with rheumatic heart disease, the lowest esophageal electrode recorded an rS pattern which was succeeded by a QS pattern localized to three leads. The atrial intrinsic deflection was absent at these levels and did not appear until several leads later. At mid-esophageal and supracardiac levels, qR and RS patterns were present, respectively (Fig. 8).

Right Ventricular Hypertrophy Without Infarction.—The ten patients in this group were selected because of electrocardiographic evidence of right ventricular

hypertrophy and fluoroscopic findings of an enlarged right ventricle. The patients had rheumatic heart disease, pulmonary disease, or congenital heart disease. In three of this group, the lower esophageal pattern was rS in configuration, and the usual transition was present at succeeding levels. The lower esophageal patterns and V_F were qR in configuration in the remaining seven. Of this latter

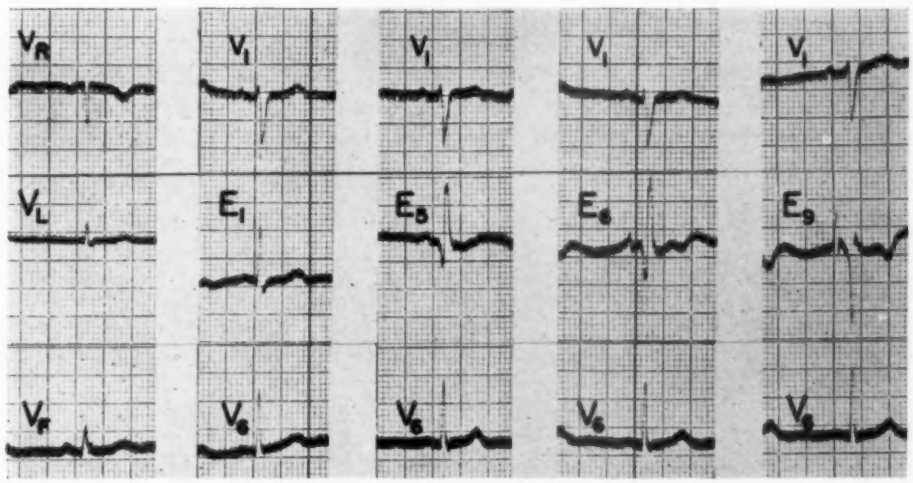


Fig. 4.—C. L., a 52-year-old white man, with no history of cardiac disease. The heart was normal on examination. (1 mv. = 10 mm.) There was an atrial intrinsic deflection in E_6 and a deep Q wave in E_5. Note the similarity of E_1 and V_F.

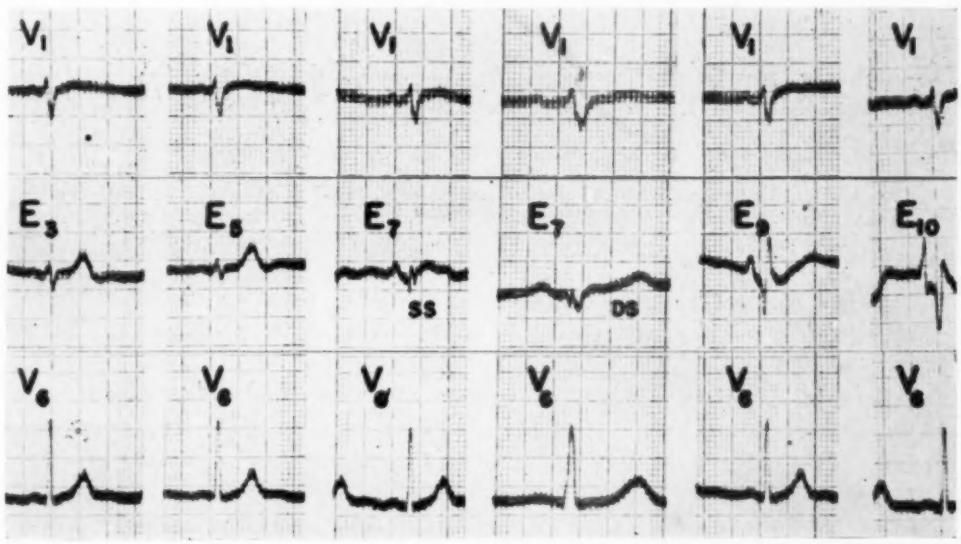


Fig. 5.—W. I., a 25-year-old white man, with no history of cardiac disease. The heart was normal on examination. The conventional leads were not remarkable. (1 mv. = 10 mm.) There was an atrial intrinsic deflection in E_{10} and a prominent Q wave in E_7 to E_9. (*SS* = record taken at normal speed; *DS* = record taken at twice normal speed.)

group, four had QS patterns localized to two or three lower esophageal electrodes prior to the appearance of an intrinsic atrial deflection (Fig. 9). At higher levels, the transition to QR, rSR, or rSr patterns with atrial intrinsic deflections occurred. At supracardiac levels, the ventricular pattern may be rSR or QR in configuration. There is a greater tendency for atrial intrinsic deflections to appear at lower esophageal levels in patients with right ventricular hypertrophy than in the other groups studied.

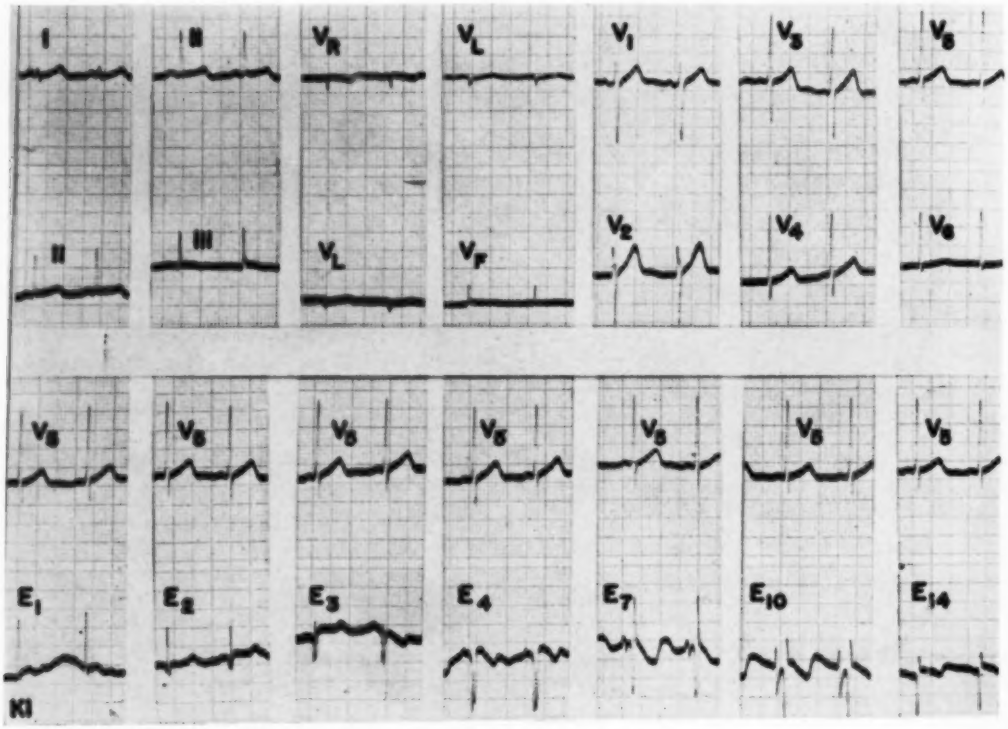


Fig. 6.—K. I., a 20-year-old white man, with no history of cardiac disease. The heart was normal on examination. (1 mv. = 10 mm.) Note the prominent Q wave in E_3 and QS in E_4 in the absence of an atrial intrinsic deflection. An atrial intrinsic deflection was present in E_7 and E_{10}. Note the similarity of E_1 and V_F.

In two cases of conspicuous right ventricular hypertrophy (one patient with Eisenmenger's complex and the other with rheumatic heart disease), precordial leads revealed a small Q wave followed by a large R wave to the right of the sternum and an absence of a Q wave to the left of the sternum. A QS pattern in the absence of an atrial intrinsic deflection was recorded at lower esophageal levels. This was replaced at the mid-esophageal level and succeeding levels by an rS pattern. One of these patients (rheumatic heart disease) was further studied by intracardiac electrocardiography performed by catheterization of the right side of the heart.[20] The pattern recorded within the right ventricle was QS in configuration, and a similar pattern was present in the mid-right auricle. At no time was the initial deflection upright in the right auricle or ventricle. In both of these cases, middle and high esophageal electrodes recorded an rSr pattern.

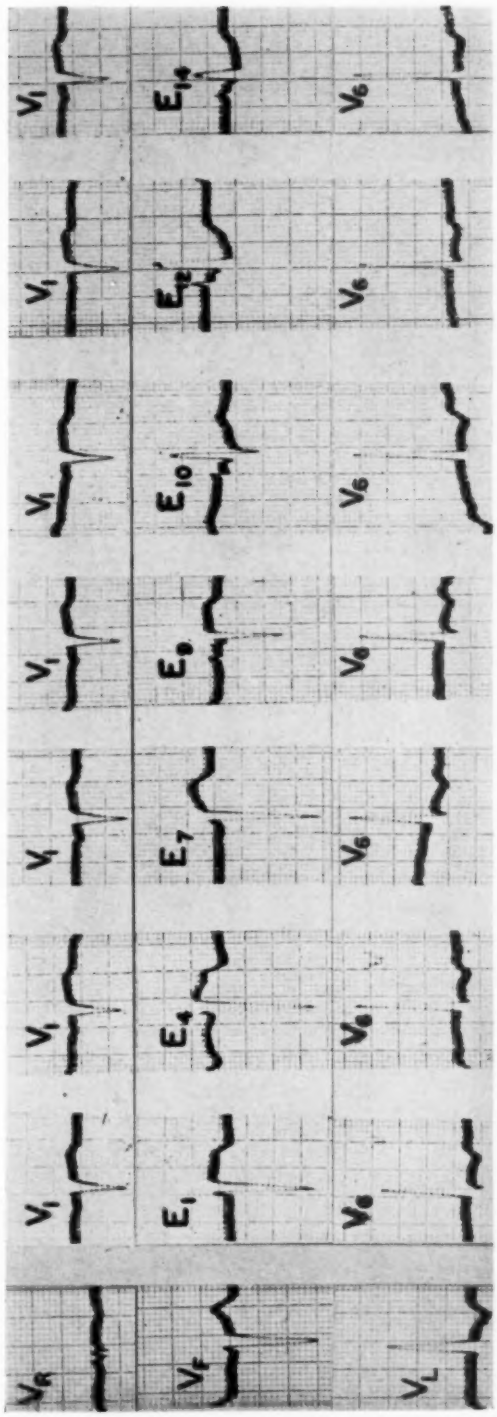


Fig. 7.—M. B., a 68-year-old white woman, with hypertension. There was marked cardiac enlargement on fluoroscopic examination. (1 mv. = 5 mm.) Note the persistence of the qR pattern in E_{14} and the similarity of E_1 and V_F.

Posterior Myocardial Infarction.—Fifteen individuals with abnormal Q waves in V_F (Q/R ratio of over 25 per cent) and histories and typical clinical courses of myocardial infarction were studied. In each instance, the pattern, as recorded in V_F, was duplicated in the leads from the lower esophageal electrodes. Lead V_F was usually recorded simultaneously with the esophageal lead and Lead III. The onset and nadir of the Q wave coincided in Leads III, V_F, and the lower esophageal lead.

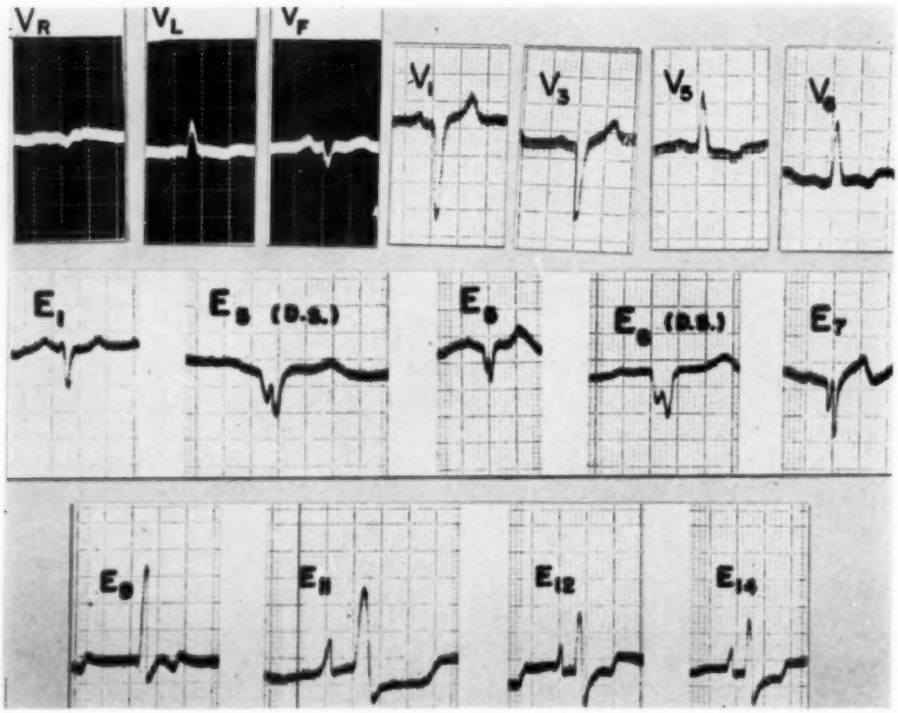


Fig. 8.—K. R., a 38-year-old Negro woman, with rheumatic heart disease. There was generalized cardiac enlargement on fluoroscopic examination. (1 mv. = 10 mm.) There was a QS pattern in E_5 to E_7 and an atrial intrinsic deflection in E_{11}. Note the similarity of E_1 to V_F. (*DS*=record taken at twice normal speed.)

In thirteen of these patients, the Q wave recorded by the lower esophageal electrodes persisted throughout the entire esophageal pattern to and including the leads at the ventricular cavity or atrial level. In these patients the transition of the ventricular pattern was such that the abnormal Q wave as recorded in the lower esophageal levels persisted until the intrinsic atrial deflection and the QS or Qr pattern of left ventricular cavity potential were recorded. At this level, the Q wave in some instances was deeper than that recorded at lower levels (Figs. 10 and 11).

In the two remaining patients in whom posterior myocardial infarction was associated with marked cardiac enlargement, the abnormal Q wave in the lower leads was replaced by a qR or R pattern at higher levels. This pattern persisted

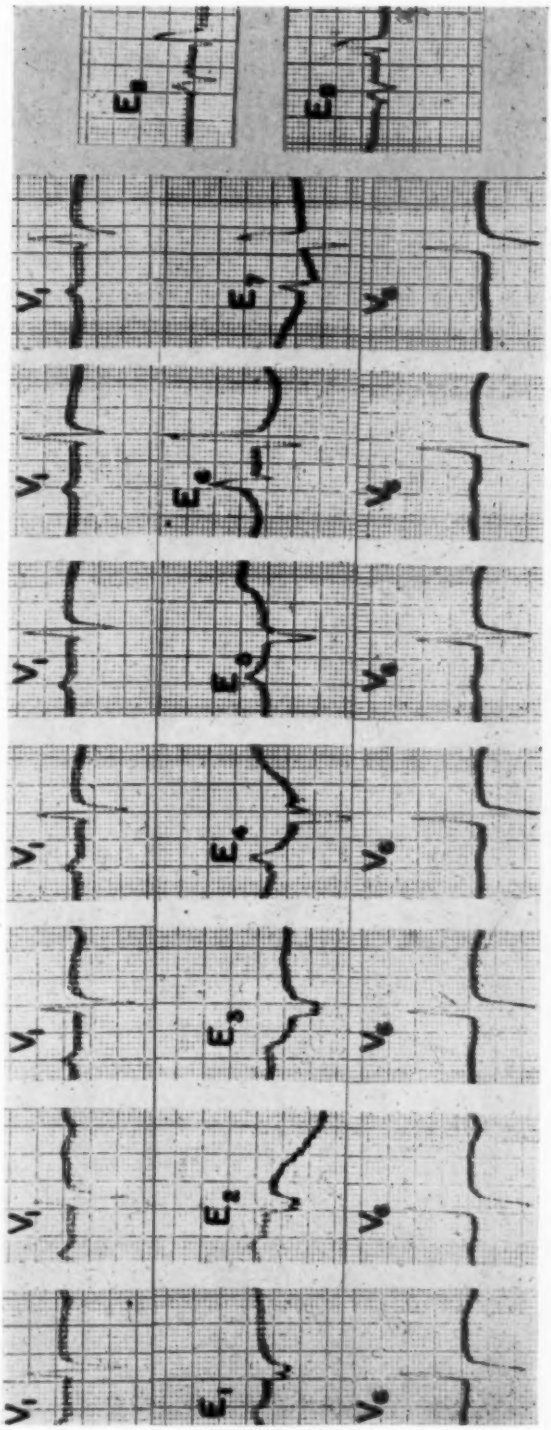


Fig. 9.—G. W., a 23-year-old white man, with Eisenmenger's complex. (1 mv. = 10 mm.) There was a QS pattern in E_1 to E_5 and an atrial intrinsic deflection in E_6. (Recorded at twice normal speed.)

despite the appearance of intrinsic atrial deflections and remained the same at supracardiac levels.

In five patients in whom borderline abnormal Q waves were present in Lead V_F, similar patterns were obtained at lower esophageal levels. The Q waves were not relatively deeper or wider until the transition and cavity zones were encountered. The esophageal leads did not reveal any additional information about the significance of the Q waves in V_F in these cases.

DISCUSSION

From this study, it is apparent that there is usually a fairly regular sequence of esophageal patterns recorded from the diaphragmatic, posterior, and supracardiac regions of the heart. However, marked deviations from the usual transitions are not infrequently encountered. For proper evaluation, an adequate esophageal electrocardiographic study requires multiple leads taken at fairly short distances along the diaphragmatic and posterior surfaces of the heart.

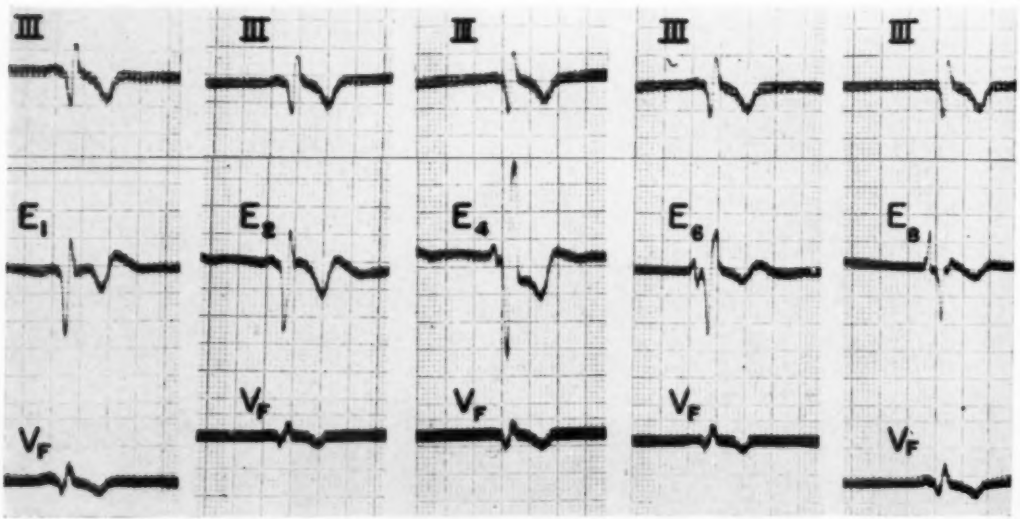


Fig. 10.—S. P., a 57-year-old white man, with posterior myocardial infarction several years previously. There was an atrial intrinsic deflection in E_4. (1 mv. = 10 mm.) There was a prominent Q wave in III, V_F, and E_1 to E_8. Note the similarity of E_1 and V_F.

Significant alterations in the esophageal electrocardiographic pattern may occur within a distance of 2 to 4 cm. Just as multiple precordial leads are of considerable aid in the careful study of precordial electrocardiographic patterns, so are multiple esophageal leads of considerable help in the analysis of esophageal electrocardiograms.

The lower esophageal electrodes reflect the potentials of the diaphragmatic and posterior surfaces of the ventricle, either right or left, depending upon the position of the heart. In the present study, the similarity of patterns obtained from the lower esophageal leads to those recorded in V_F was a constant finding regardless of the size or configuration of the heart. Other investigators have

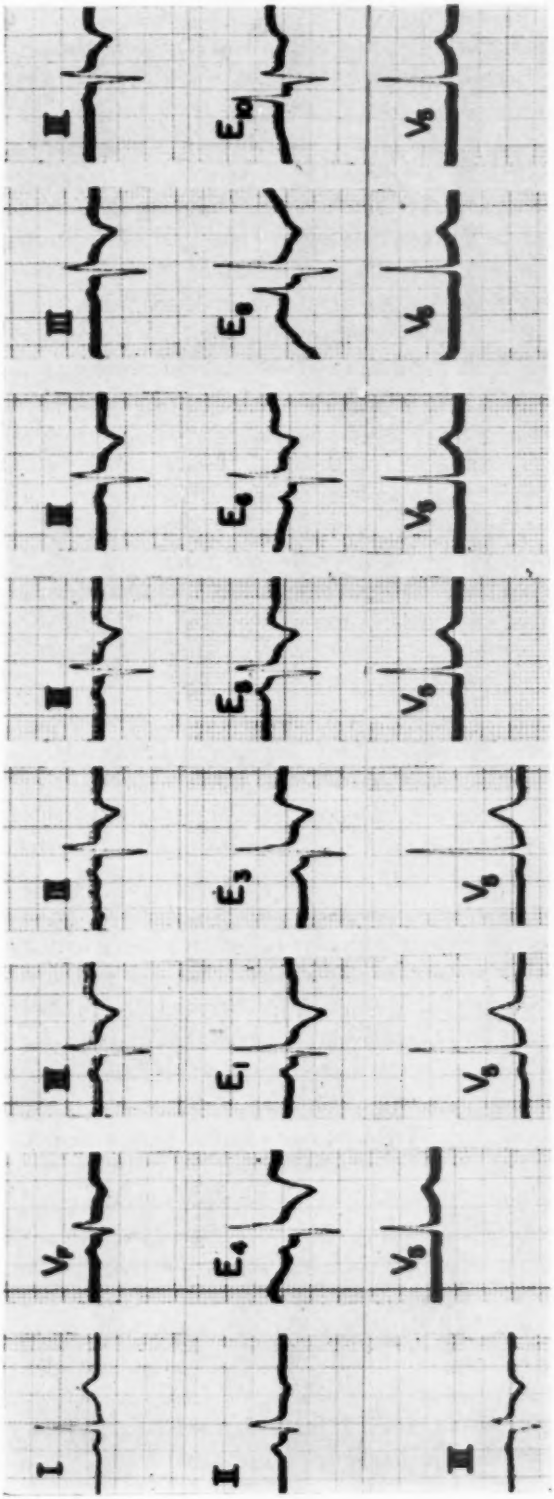


Fig. 11.—F. C., a 66-year-old white man, with posterior myocardial infarction several years previously. (1 mv. = 10 mm. except for V_5 recorded at 5 mm. with E_4 and at 7 mm. with E_5 to E_{10}.) There was an atrial intrinsic deflection in E_8 and a prominent Q wave in III, V_F, and E_1 to E_{10}. Note the similarity of E_1 and V_F.

demonstrated that V_F reflects the potential of the diaphragmatic surface of the heart.[9,11,21,22] With the distal electrode well in the stomach, the records obtained in this position reflected the diaphragmatic surface and were similar to V_F.

At a variable distance from the diaphragm, but usually at a distance of 5 to 10 cm., the ventricular surface pattern, which has usually been rS or qR in configuration, is succeeded by a QS or Qr pattern which represents essentially left ventricular cavity potentials. QS patterns have been obtained in the left ventricle of dogs by intracardiac electrodes[23,24,25] and in the left ventricle of human beings by catheterization of the left side of the heart.[26] Other investigators[4,8,9,21,27] had noted that esophageal electrodes at a certain level will reflect potentials of the left ventricular cavity. Application of this fact has permitted studies to be carried out upon the RS-T segment deviations occurring within the left ventricle in coronary insufficiency,[19] left ventricular hypertrophy, bundle branch block, and during digitalis therapy.[28] Caution should be exercised in the proper selection of the esophageal lead best reflecting left ventricular cavity potential. The onset of the Q wave of the esophageal lead must be earlier than, or simultaneous with, any other ventricular deflection in a simultaneously recorded lead, and the pattern should be QS or Qr in configuration.

Usually, but by no means always, the atrial intrinsic deflection is present when the ventricular complex is QS in configuration. The P wave, which had been upright and of low amplitude in the lower esophageal levels, has become diphasic, of increased amplitude, and has developed a sharp downward or intrinsic deflection. However, the transitional zone between ventricular surface and ventricular cavity varies considerably in position and length and is markedly influenced by the size of the heart and its anatomical position. The appearance of ventricular cavity potential may precede the appearance of the atrial intrinsic deflection by several centimeters, and the opposite may also occur.

The presence of an atrial intrinsic deflection has been suggested as indicating that the ventricular complex recorded represents ventricular cavity potential; and, in its absence, the ventricular complex represents ventricular surface potential. The results of the present study reveal that such a correlation is not constant. It is also evident that the use of prescribed distances[8,10,11,29] from the nares to the electrode to establish atrial and ventricular levels does not lend itself to accurate localization of the esophageal electrode. The wide range in individual height and the variability of cardiac size and of cardiac position within the thorax prevent rigid criteria from being prescribed as to atrial and ventricular levels.

In left ventricular hypertrophy, the transition from ventricular surface to ventricular cavity potentials follows the usual sequence, unless marked cardiac enlargement is present. Left ventricular cavity potentials may never be tapped in such instances, and the ventricular complex may remain qR and resemble V_6 in configuration. It is believed that the esophageal electrode is so situated in such cases as to record predominantly left ventricular surface potential even at mid-esophageal and supra-atrial levels. Marked cardiac enlargement was associated with posterior myocardial infarction in two patients of the present series. The abnormal Q wave in the lower esophageal leads in these patients was

replaced by a qR or R pattern at higher levels, and V_R was qR in configuration. In these two patients, it is possible that the high esophageal and V_R patterns were due to unbalanced ventricular surface potentials due to disruption of the usual balance of electromotive forces.

In right ventricular hypertrophy, there is a tendency for atrial intrinsic deflections to appear at lower esophageal levels than in the other groups studied. Isolated leads occasionally revealed QS patterns several centimeters prior to the appearance of the atrial intrinsic deflection. In some of the patients of the present series, the similarity of intracardiac electrocardiograms as obtained in right ventricular catheterization[20] to those recorded in the lower esophageal levels strongly suggests that right side potentials may occasionally be tapped through the inferior vena cava or right atrium.

In one patient with right ventricular hypertrophy, a QS pattern at lower esophageal levels was succeeded by an rS pattern at mid-esophageal and higher levels. Precordial leads revealed a small Q wave followed by a large R wave to the right of the sternum and the absence of a Q wave to the left. Catheterization of the right side of the heart revealed a QS pattern to be present in the right ventricle and right auricle. Other investigators[30,31] also found QS patterns in the right ventricle in instances of right ventricular hypertrophy and have ascribed this finding to various causes. It is quite likely that the initial negativity as recorded in V_1, the lower esophageal leads, and in the electrocardiograms recorded from within the right ventricle represents a change in the balance of electromotive forces from that usually found during activation of the septum, so that the initial positivity recorded is now directed to the left rather than to the right. The registration in this case of a small R wave at the higher esophageal levels, which probably represent left ventricular cavity potentials, would tend to confirm this interpretation.

Of considerable aid in this study was the simultaneous recording of three different leads. A cavity or septal Q wave should precede or be simultaneous with any other ventricular deflection in a simultaneously recorded lead. This is also true as far as the Q wave in posterior infarction is concerned. In an occasional electrocardiogram recorded by an electrode in the lower esophagus of patients without infarction, an apparent QS pattern was obtained in which the initial downward deflection occurred as long as 0.03 second later than the R or Q waves in simultaneously recorded precordial electrocardiograms. This delay may be due to potentials moving perpendicular to the esophageal electrode so that the initial position of the ventricular complex is recorded as an isoelectric line. Such a pattern cannot be attributed to infarction, although its appearance in an isolated electrocardiogram would certainly suggest cavity potential. In any electrocardiographic study which requires the positive identification and timing of initial deflections, simultaneously recorded electrocardiograms are of definite value. In addition, the ventricular intrinsic deflection can be used to compare the activation of the precordial, diaphragmatic, and posterior surfaces of the heart.

Multiple precordial leads have been extremely helpful in the diagnosis and localization of anterior wall infarctions. However, more difficulty has

been encountered in the instance of posterior wall infarction. It is generally accepted that V_F is more reliable than standard Lead III,[11] and, more recently, esophageal leads have been employed as an adjuvant in diagnosis.[6-9,11,22] While infarctions of the left ventricular surface contiguous to the diaphragm are reflected in V_F,[9,15] the diagnosis and localization of infarctions of the left ventricular surface lying posterior and away from the diaphragm have remained a problem. Esophageal electrocardiography has been used to explore the posterior and diaphragmatic surface of the heart especially when the right ventricle rests upon the diaphragm, or when infarctions localized to the infra-atrial zone are suspected and V_F is not remarkable in configuration.[9,15]

The patients included in this study of posterior myocardial infarction were selected because of abnormal Q waves in V_F and a typical clinical course of myocardial infarction. The similarity of patterns obtained from the lower esophageal leads to those recorded in V_F was a constant finding, regardless of the size or configuration of the heart and of the presence or absence of a posterior myocardial infarction. When an abnormal Q wave was present in V_F, a similar pattern was recorded by the lower esophageal electrodes. Usually, the Q wave recorded by the lower esophageal electrodes persisted throughout the entire esophageal pattern to and including the leads at the ventricular cavity or atrial level. The essential similarity of the electrocardiographic pattern at the lower esophageal levels to that recorded at the atrial level would indicate that both the infarcted area and the atrial leads reflect left ventricular cavity potential, the former through the window effect[32] of the electrically dead tissue and the latter because of left ventricular cavity potential reflected to the electrode contiguous to the left atrial surface.

In a few patients whose electrocardiograms demonstrated borderline abnormal Q waves in V_F, similar tracings were obtained in multiple leads from the lower esophageal levels. No additional information was secured to aid in the evaluation of the Q wave in V_F.

If there is no evidence of infarction in the standard extremity, unipolar precordial, or unipolar extremity leads and a Q wave is found in esophageal leads at infra-atrial levels, the interpretation of this finding requires much caution. It is in the transition area in particular that Q waves considered diagnostic of posterior infarction by some criteria may be recorded. Multiple esophageal leads, however, as utilized in the present study, reveal that such findings are not too reliable because of the variability of the level at which the atrial intrinsic deflection and ventricular cavity potential may make their appearance in normal-sized as well as hypertrophied hearts. Hence, the diagnosis of a localized posterior myocardial infarction by the registration of a Q wave at ventricular or infra-atrial levels, as defined either by distance from the nares to the electrode or by absence of an intrinsic atrial deflection, should be made with great caution.[17] This is shown by the occurrence of wide or deep Q waves in the transition zone of normal patients in this series prior to the appearance of an atrial intrinsic deflection.

Of possible significance in cases of suspected infarction would be the recording at lower esophageal levels of a QS or Qr pattern localized to one or two

esophageal leads and absent in the others. Such a pattern might theoretically be considered similar to the finding of a localized anterior or anteroseptal infarction wherein the precordial transition is suddenly interrupted. In none of our patients with known posterior myocardial infarction was an abnormal pattern localized to but a few esophageal levels. The full evaluation of an interruption in the usual transition of an esophageal pattern by the appearance of an isolated abnormal Q wave must depend not only upon the complete esophageal pattern but also upon the realization that an apparently abnormal QS or Qr configuration may be recorded in isolated leads in individuals with normal-sized or enlarged hearts without infarction. Contiguity of the esophageal tube to the inferior vena cava or right atrium has been demonstrated,[20] and a localized QS or Qr pattern may represent right cavity potential recorded by the esophageal electrode. Intracardiac catheterization in two patients revealed that the QS or Qr patterns recorded at localized esophageal levels were probably due to inferior vena cava or right atrial potentials. The possibility that such an interruption in the expected transition may occasionally represent localized posterior myocardial infarction exists, but it is difficult to prove. The results of this study are similar to those of others[16,17] in demonstrating the difficulty of interpreting a Qr or QS pattern in esophageal leads, especially in the absence of characteristic changes in V_F.

In precordial electrocardiography, the presence of a Q wave is ascribable either to septal activation or myocardial infarction, and the electrode lies over either the right or left ventricular surface. However, the esophageal electrodes may be contiguous to many different areas, including left ventricle, left auricle, right ventricle, right auricle, inferior vena cava, and the great vessels. While the auricular complex does follow a uniform transition from patient to patient, the ventricular complex varies considerably, depending upon the size of the heart and its position within the thorax. Usually, the transition from ventricular surface to ventricular cavity in a heart of normal size is rather regular. Yet, at any one level, the contribution of cavity or surface to the ventricular complex pattern may be difficult to evaluate. More extensive application of multiple esophageal leads will aid in the interpretation of the complete esophageal electrocardiographic pattern.

Esophageal electrocardiography has permitted the recording of potentials arising from portions of the heart otherwise inaccessible for detailed study. The contiguity of the esophagus to the left atrium allows the recording of prominent atrial complexes and affords an excellent method for the analysis of arrhythmias in which the identification of atrial complexes in the usual leads is difficult or impossible. Left ventricular cavity potential is tapped by the electrode lying adjacent to the left atrium, and this approach has recently been applied to the study of RS-T segment deviations in various conditions.[19,28] It is hoped that a wider employment of esophageal electrocardiography will be of assistance in other clinical electrocardiographic problems.

SUMMARY

1. The esophageal patterns recorded by multiple esophageal electrodes are described in normal and hypertrophied hearts and in posterior infarction.
2. There is a definite transition zone in which the electrocardiographic pattern changes from that representing ventricular surface to that reflecting left ventricular cavity.
3. In this zone there is a variability as to the levels of appearance of ventricular surface and ventricular cavity potentials and of the atrial intrinsic deflections.
4. Lead V_F and the lower esophageal leads consistently reflect the electrocardiographic pattern of the diaphragmatic surface of the heart, both in normal patients and in those with infarction.
5. The application of esophageal electrocardiography in the diagnosis of localized posterior myocardial infarction is discussed.

We wish to express our thanks to Dr. Arthur M. Master for his cooperation in making this study possible.

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FACTORS INFLUENCING THE T WAVE OF THE ELECTROCARDIOGRAM

III. Nonchronotropic T Changes Produced by Acetylcholine

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IN 1906, Hunt and Taveau[1] showed that acetylcholine is effective in minute doses, and, in 1914, Dale[2] divided these effects into the muscarinic and nicotinic types. The muscarinic action is peripheral, acting on the end organ itself. It can be completely abolished by atropine. Whether or not it is abolished by atropine, another effect, the nicotinic action, becomes evident later. This action is on the ganglion cells. In the cardiovascular system the muscarinic effect is one of depression.[1-8] The nicotinic action is one of stimulation.[8-11]

Wedd,[5] working with dogs, used acetylcholine in doses of 0.01 mg. and greater and noted that in every instance there was a prompt fall in blood pressure. Goldenberg and Rothberger[12] and, subsequently, other groups of workers[6,10,11,13] described the changes in the electrocardiogram of the dog. In brief, these consist of decrease in height, notching and diphasic character of P, T_a (auricular T) depression, varying degrees of block including complete standstill, auricular fibrillation, increased amplitude of T, and premature beats of varying origin. The amounts of acetylcholine used in these experiments ranged from 1.0 to 7.0 mg. In a recent report Callebaut, Rodbard, and Katz[22] produced atrioventricular block with 20 to 80 μg when given with a catheter directly to the region of the coronary ostia.

In the course of experiments on the genesis of the T wave,[14] we became interested in the effects of acetylcholine on the electrocardiogram of the dog. We are reporting our results for the following reasons: (a) Both intracavitary and extracavitary leads were employed, probably for the first time in an acetylcholine study; (b) electrocardiographic and blood pressure studies were conducted simultaneously so as to clarify the time relations between the early electrocardiographic changes and the blood pressure; (c) we re-emphasized the effectiveness of minute doses of acetylcholine; (d) on the basis of our findings the factors concerned in the genesis of the T wave were discussed further.

METHOD

A total of fifteen dogs was used. All were anesthetized with Nembutal, approximately 25 mg. per kilogram. In the initial experiments on eight dogs, the

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A preliminary report was presented at the Proceedings of the American Physiological Society, March, 1950 (Federation Proc. 9:77, 1950).

Aided in part by a grant from the Youngstown Heart Association.

Received for publication Aug. 9, 1950.

acetylcholine* was given by way of the jugular vein in volumes ranging from 0.01 c.c. to 1.0 c.c. Seventy-eight such injections were made. No blood pressures were recorded. In two of these animals injections were made under local anesthesia before general anesthesia was given for purposes of comparison with results obtained following general anesthesia. In the subsequent experiments on seven dogs, the acetylcholine was injected in 5 c.c. amounts. Intracardiac injections were through a catheter tip placed at the superior vena caval-right auricular junction via a jugular vein. Seventy-one such injections were made. Intra-arterial injections were through a catheter tip placed in the mid-descending thoracic aorta by way of a femoral artery. Thirty such injections were made. After each injection the catheter was flushed with saline. Control experiments consisted of the injection of equal quantities of saline by the same routes as above. There were no significant changes in the electrocardiogram. Occasionally the blood pressure rose several millimeters at the end of the injection. Continuous blood pressure readings were recorded on a kymograph by means of a mercury manometer from the opposite femoral artery.

Right intracavitary leads, both auricular and ventricular, were recorded from an electrode passed through a jugular vein. Left intracavitary leads were recorded from an electrode passed through a carotid artery. The extracavitary leads were made in the usual manner and included standard and augmented "unipolar" limb leads and "unipolar" precordial leads. The Wilson central terminal was used as the indifferent electrode.

All blood pressure and electrocardiographic changes caused by the acetylcholine were temporary and recovery was always complete. For this reason multiple experiments could be performed on the same animal.

RESULTS

The effectiveness of a given dose of acetylcholine varied from animal to animal but was extremely constant in any given animal. In any one dog the blood pressure fall was approximately proportional to the amount of acetylcholine given. Simiarly the electrocardiographic changes increased in type and duration with increase in dose. The various types of electrocardiographic changes described in detail by others[6,11-13] were observed. Only the T-wave changes, ventricular (hereafter called T) and auricular (hereafter called T_a), will be discussed in this report.

Cardiac arrhythmia (atrioventricular block, complete standstill, auricular fibrillation) could always be caused by intracardiac injections of acetylcholine if sufficiently large doses were given. Intra-arterial injections of the same amounts, however, never resulted in such electrocardiographic change even if the degree of blood pressure fall was comparable to that caused by the intracardiac injection.

Blood Pressure.—The time of onset of blood pressure response in relation to the time of acetylcholine injection was fairly constant in a given animal

*All acetylcholine used in this study was crystalline acetylcholine chloride supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

regardless of the amount of acetylcholine given. The intra-arterial route of administration usually resulted in earlier blood pressure fall than the intracardiac route.

Two patterns of blood pressure response were seen in relation to the intra-arterial versus the intracardiac routes of administration of acetylcholine. In one pattern the blood pressure fall was always slightly greater by the intra-arterial route as the dose was increased until the point at which a sufficiently large dose (and, of course, all larger doses) caused cardiac arrhythmia. From that point on the blood pressure fall was greater when acetylcholine was administered into the heart (Fig. 1). In the second pattern the intra-arterial route resulted in a greater blood pressure fall than the intracardiac route with the more minute doses. With larger doses, even with persisting regular sinus rhythm,

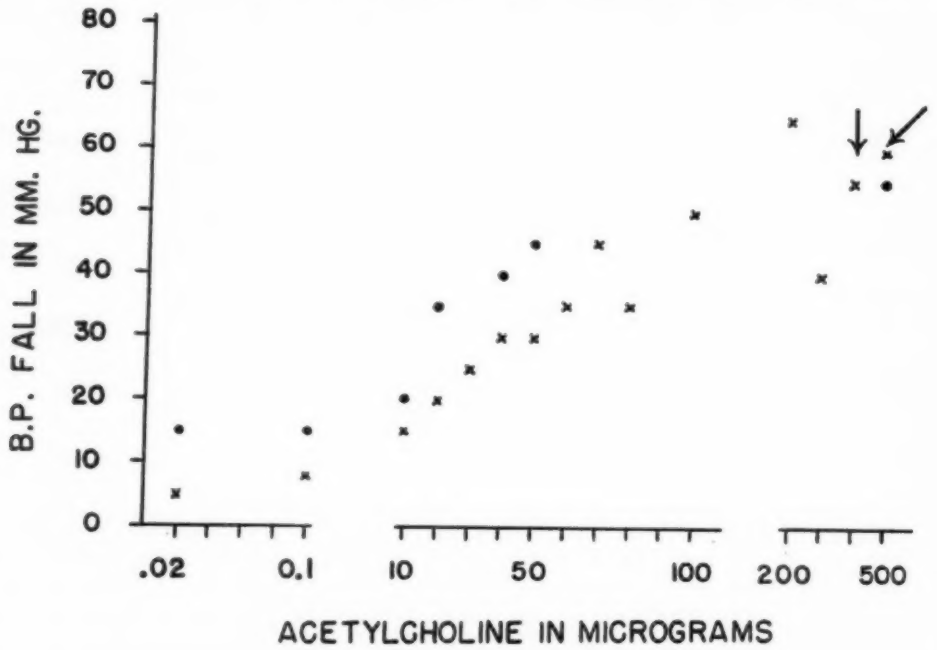

Fig. 1.—Relation of fall in blood pressure to dose of acetylcholine and route of administration. Dots represent intra-arterial injection. Crosses represent intracardiac injection. Vertical arrow: intracardiac injection caused sinoauricular block for one beat. Slanting arrow: intracardiac injection caused sinoauricular block followed by auricular fibrillation. Intra-arterial injections did not cause any arrhythmia. Discussed in text.

the intracardiac route caused a greater fall of blood pressure. This continued, of course, with the even larger doses that resulted in cardiac arrhythmia (Fig. 2).

Effect of Minute Doses.—In the experiments reported in the American literature[6,10,11,13] acetylcholine was injected in amounts ranging from 1.0 to 7.0 mg. Our results re-emphasize the effectiveness of much smaller doses in the intact animal. As will be shown below, the blood pressure and early electrocardiographic changes following the injection of acetylcholine are independent of each other. For this reason the smallest doses resulting in fall of blood pressure and

in electrocardiographic change are given separately. The smallest amount of acetylcholine which caused a blood pressure fall was 0.01 μg. This dose was effective in a dog which weighed 12 kilograms. Intra-arterial injection resulted in a blood pressure fall of 25 mm. Hg, and intracardiac injection was followed by a fall of 20 mm. Hg.

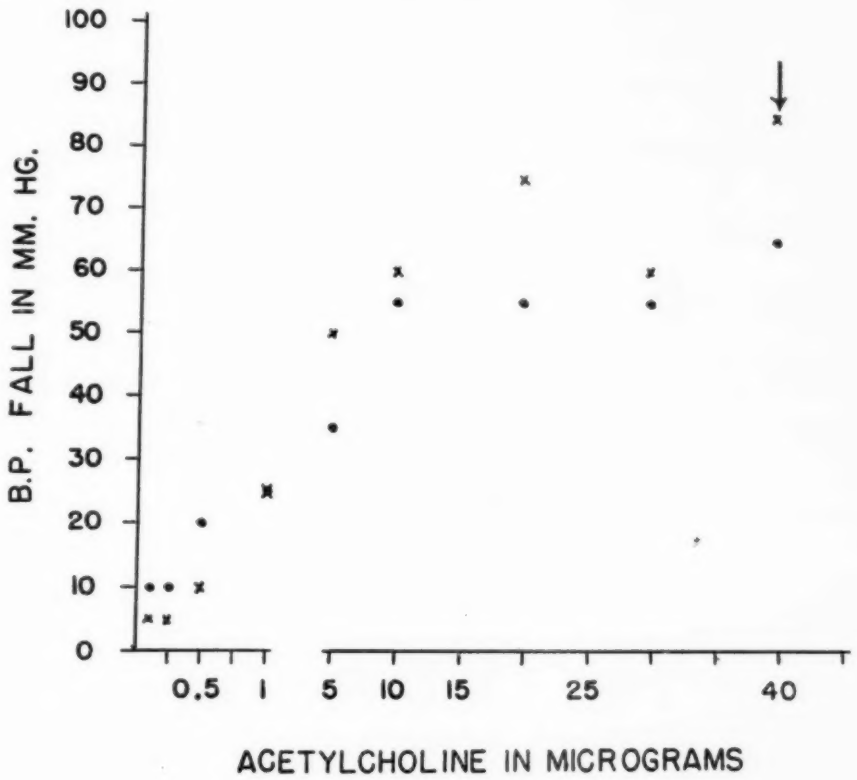

Fig. 2.—Relation of fall in blood pressure to dose of acetylcholine and route of administration. Dots represent intra-arterial injection. Crosses represent intracardiac injection. Vertical arrow: intracardiac injection caused complete atrioventricular block. Intra-arterial injection did not cause any arrhythmia. Discussed in text.

The smallest amount of acetylcholine which caused T-wave change was 5 μg (in an 8 kilogram dog). The minimal dose which resulted in T_a change was 0.1 μg in a 9 kilogram dog. In general, however, the same minimal amount resulted in both T and T_a change in a given dog. The figures just mentioned plus the minimal doses causing other electrocardiographic changes are shown in Table I.

Relation of Intra- and Extracavitary T Waves.—Acetylcholine produced a change in the direction of the T wave, i. e., it altered the direction of ventricular repolarization. The expected reciprocal relationship of this T-wave change as seen in extra- and intracavitary leads[14] was noted (Figs. 3 and 4). The T waves became absolutely or relatively positive in the epicardial and precordial leads

over the left ventricle and absolutely or relatively negative in the leads reflecting cavity potentials (intraventricular and intra-atrial leads).

TABLE I.

EFFECT NOTED	MINIMAL DOSE IN MICROGRAMS	WEIGHT OF DOG IN KILOGRAMS
T_a change	0.1	9
T change	5.0	8
Atrioventricular block	40.0	8
Complete standstill	50.0	9.8
Auricular fibrillation	500.0	13.0

There was a similar relationship in the change of direction of the auricular T wave. Fig. 5 shows depression of T_a in Lead aV_F, an extracavitary lead, following an injection of acetylcholine. Lead aV_R (Fig. 6), whose electrical potential is that of the negative field of the right ventricular cavity, shows T_a elevation.

Electrocardiographic Change in Relation to Route of Administration of Acetylcholine.—As already mentioned, intra-arterial acetylcholine did not disturb the cardiac mechanism. The only significant finding was an occasional late primary T-wave change associated with a fall of blood pressure. The T wave became relatively or absolutely more negative in extracavitary leads. There were no T_a changes.

On the other hand, intracardiac acetylcholine produced not only late T changes but also arrhythmias, T_a and early T alterations. Therefore, in subsequent discussion, the changes in T and T_a are those resulting from intracardiac acetylcholine.

T_a and T Change.—T_a depression, in extracavitary leads, occurred frequently following the injection of acetylcholine. Significantly, this electrocardiographic alteration usually occurred independently of blood pressure change. T_a depression was seen in thirty-one out of thirty-four instances before or without fall of blood pressure. If blood pressure did fall, the depression of auricular T began before the fall, reached its maximum before or during the fall, and even returned to control before the time of maximal blood pressure decrease (Fig. 5). The same time relationship of T_a elevation in aV_R is shown in Fig. 6. Fig. 7 shows even more clearly the complete independence of T_a change from blood pressure change. Here a minute dose of acetylcholine (0.1 μg) resulted in T_a depression but no drop in blood pressure.

Similarly, though less frequently, early T changes were observed. Of thirty-one instances of T change (increased amplitude in aV_F; decreased amplitude in aV_R) such change was seen nine times before, or without, fall of blood pressure. It occurred with the same independence of the mean blood pressure as did alteration of T_a and, in fact, took place more quickly and recovered more quickly (Figs. 5, 6, and 7). It is to be emphasized that all the above T_a changes occurred not only without relation to the decrease in blood pressure but also in the absence of any of the chronotropic effects (tachycardia, atrioventricular block, auricular fibrillation) described by previous authors. Fig. 10 illustrates that even in the

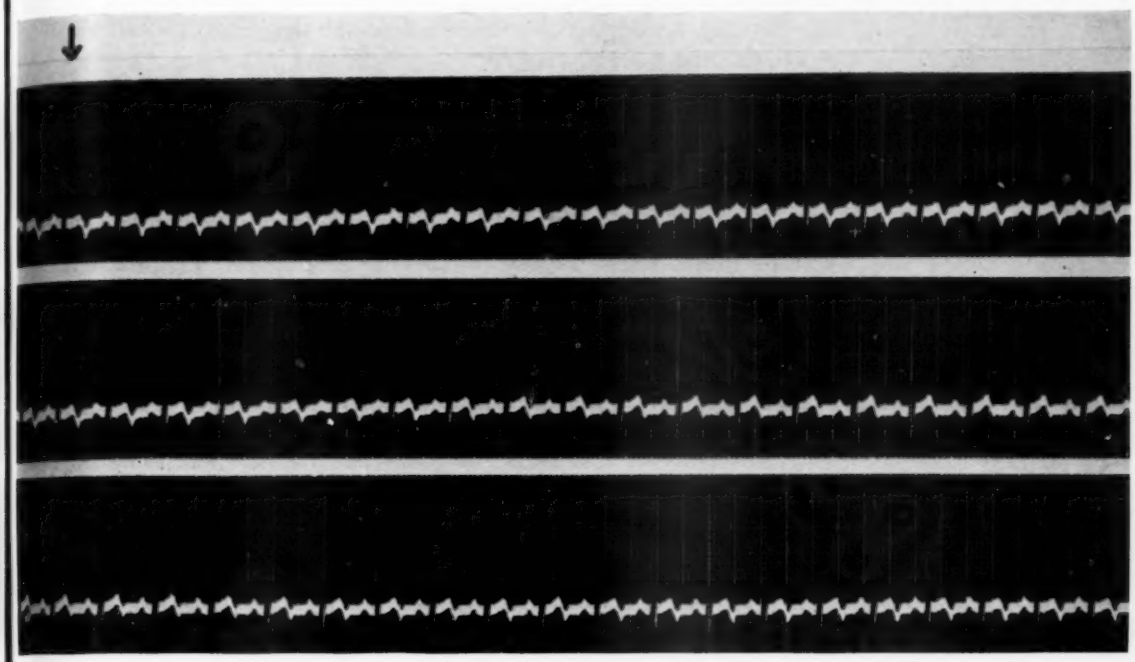

Fig. 3.—Lead from apex of left ventricle. Arrow indicates time at which 0.1 mg. of acetylcholine was injected into a jugular vein. Note resulting positivity of extracavitary T without change in heart rate.

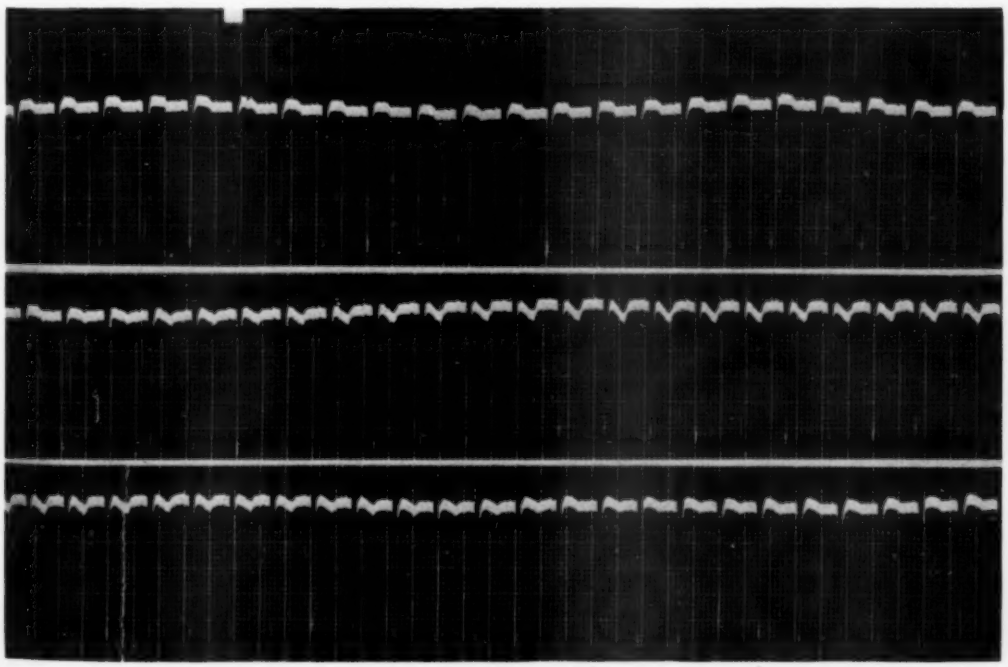

Fig. 4.—Lead from cavity of left ventricle. Marker indicates time at which 1 mg. of acetylcholine was injected into a jugular vein. Note resulting increase in negativity of intracavitary T without change in heart rate.

presence of chronotropic effect, the primary T-wave change described precedes the onset of the altered cardiac mechanism.

An interesting combination of T_a changes was seen in the lead taken from the superior vena caval-right auricular junction in the region of the sinoauricular node. In this lead an injection of acetylcholine resulted in gradual but appreciable T_a depression which was then rapidly succeeded (within three or four complexes) by a marked T_a elevation (Fig. 8). Both changes occurred in the absence of chronotropic effect and changes in respiration. At the time of the late slight positive chronotropic effect that frequently appeared, the T_a segment had already returned to control.

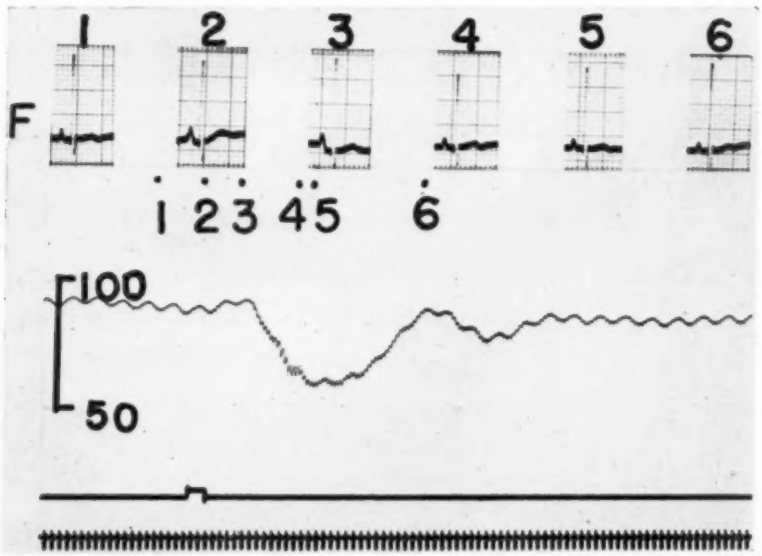

Fig. 5.—Relationship of T_a and T alteration to change in blood pressure. Forty μg of acetylcholine injected into the right atrium. Bottom to top: Line 1—time in seconds; line 2—marker denoting beginning, duration, and end of injection; line 3—mean blood pressure in mm. Hg; line 4—each dot, in order, represents the respective segment of electrocardiogram in line 5; line 5—Lead aV_F. A vertical line dropped from each dot would give the time relationship of the respective electrocardiographic segment to the level of blood pressure and the time of injection. Dot *1*: control. Dot *2*: 1.8 seconds after the beginning of injection. T_a is depressed. Maximum increase of positive T is already evident. Blood pressure is unchanged. Dot *3*: 7 seconds after the beginning of injection. T_a depression is maximum. T is returning to control. Blood pressure remains unchanged. Dot *4*: 14.5 seconds. T_a and T are back to control. Blood pressure is now falling. Dot *5*: 16.5 seconds. Maximum fall in blood pressure. T_a and T remain unchanged at control levels. Dot *6*: 32 seconds. Blood pressure is back to control level. T_a and T have remained unchanged during the fall in blood pressure. There was no change in heart rate.

Cardiovascular Changes in Relation to the Amount of Acetylcholine.—As the dose of acetylcholine was increased, the cardiovascular changes became more numerous and more marked. As the amounts of acetylcholine were gradually increased, a fall in blood pressure was usually the first indication that the smallest physiologically effective dose had been given. As stated previously, when the dose was subsequently increased, the fall in blood pressure became greater in an approximately proportionate manner.

Infrequently T and T_a changes were the first indication that the smallest physiologically effective dose had been given. Usually, however, these changes occurred only with doses larger than those necessary to produce a fall in blood pressure. This is not to be confused with the fact that when the dose was sufficiently large as to cause both the fall in blood pressure and the change in repolarization, the latter usually occurred first chronologically.

With successively larger doses the chronotropic effects appeared. They did so in the following order: first, a delayed increase in rate in the absence of other chronotropic effect (reflex, from the fall in blood pressure, or nicotinic effect); second, atrioventricular block; third, complete standstill; and fourth, auricular fibrillation. The last three arrhythmias often occurred in combination. If they did, they did so in the above order. Recovery from the arrhythmias was usually succeeded by an increase in rate, probably for one or both of the reasons cited.

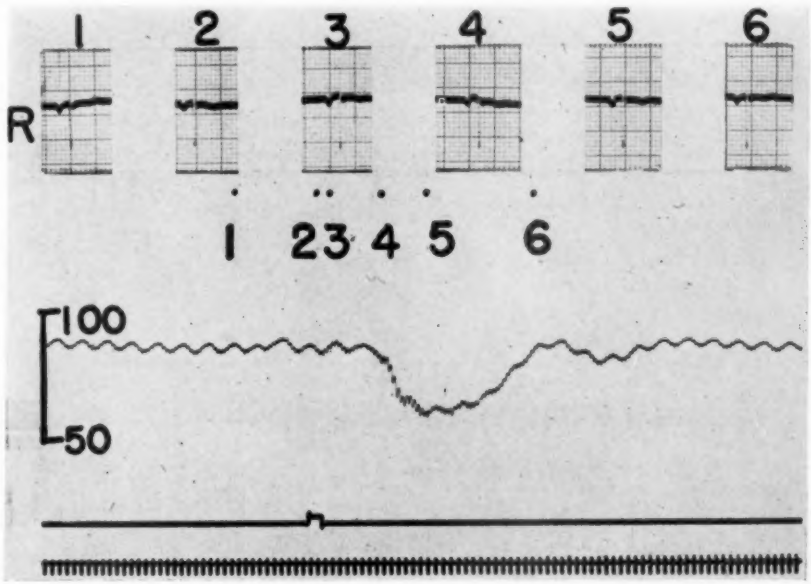

Fig. 6.—Relationship of T_a and T alteration to change in blood pressure. Fifty μg of acetylcholine injected into the right atrium. This figure has the same arrangement as Fig. 5. Line 5—Lead aV_R. Dot *1*: control. Dot *2*: 1.5 seconds after the beginning of injection. T has changed from upright to inverted. T_a is unchanged. Blood pressure is unchanged. Dot *3*: 2.5 seconds after the beginning of injection. T is still negative. T_a is now elevated. Blood pressure remains unchanged. Dot *4*: 9 seconds. Fall in blood pressure is just beginning. T is still negative, and T_a is still elevated but both are returning to control levels. Dot *5*: 16 seconds. Fall in blood pressure is now maximum, but T is now diphasic and T_a is back to control. Dot *6*: 30 seconds. Blood pressure has just reached control level. T and T_a are back to control. There was no change in heart rate.

Comparison of Results With and Without General Anesthesia.—As described above, acetylcholine injected into anesthetized dogs resulted in early increased negativity of the intracavitary T (Figs. 4 and 8) which returned to control before or during the moderate tachycardia of the late nicotinic effect. No late T change was associated with the tachycardia. Atrioventricular block occurred with sufficiently large doses.

In the unanesthetized dog the early T change was not noted. The positive chronotropic effect of the nicotinic stage was more marked than in the anesthetized dog, however, and during this marked tachycardia a delayed T change was seen. This change was in the opposite direction: negative intracavitary T became less negative and even upright (Fig. 9). Larger doses of acetylcholine produced a similar degree of atrioventricular block in both anesthetized and unanesthetized animals.

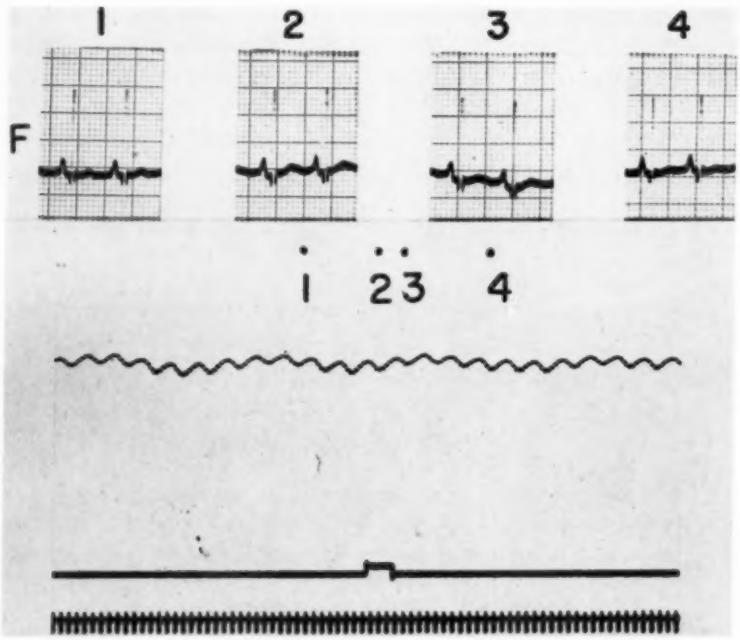

Fig. 7.—T and T_a change in the absence of fall in blood pressure. 0.1 μg of acetylcholine injected into the right atrium. This figure has the same arrangement as Figs. 5 and 6. Line 5 is Lead aV_F. Dot *1*: control. Dot *2*: 1 second after the beginning of injection. T_a is already depressed. T has reached maximum increase in positivity. The blood pressure is unchanged. Dot *3*: 4.5 seconds. T_a depression is maximum. T is returning to control. The blood pressure is unchanged. Dot *4*: 15 seconds. T_a and T are at control levels. There was no change in blood pressure at any time. There was no change in heart rate.

DISCUSSION

The site of injection of acetylcholine bears a relation to its effect. The intra-arterial injection resulted only in fall in blood pressure (and occasional late reflex increase in heart rate) with no early electrocardiographic changes. Injection into the mid-abdominal aorta was obviously quickly effective on the peripheral arteries, causing fall in blood pressure. But such intra-arterial injection resulted in no electrocardiographic change, probably because of rapid hydrolysis of acetylcholine by serum cholinesterase and dilution in the pulmonary circuit. Thus no acetylcholine reached the coronary arteries. Wilburne and associates[3] have shown that the changes in the electrocardiogram occur only when acetylcholine enters the coronary arteries. Injection into a peripheral

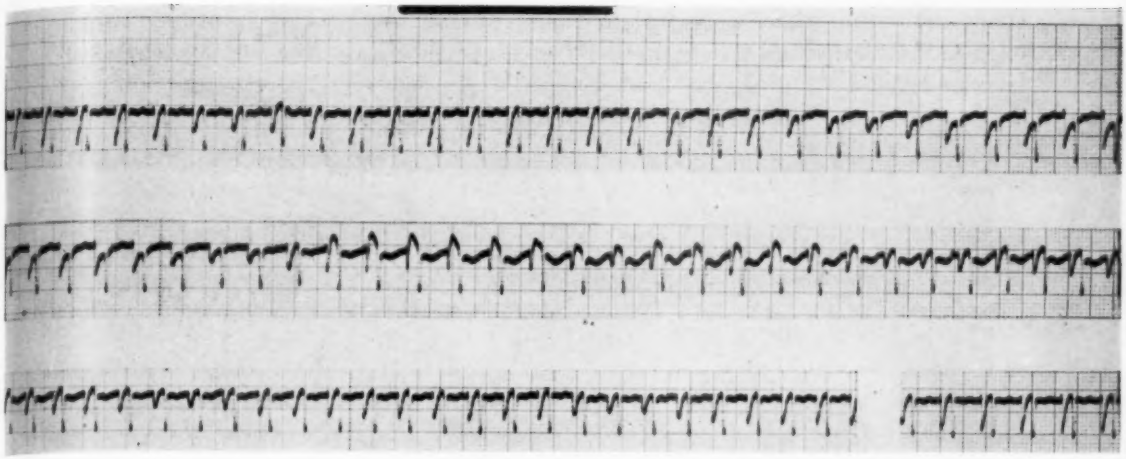

Fig. 8.—Exploring intracavitary electrode is located at the junction of the superior vena cava and the right atrium. One mg. of acetylcholine was injected into a jugular vein. The beginning and duration of injection are denoted by the horizontal black line in the upper margin of the top strip. This is a continuous record; the last segment was taken two minutes after the injection. Note the initial gradual T_a depression, rapidly succeeded by marked T_a elevation. T becomes inverted and then returns to control. During the period of these changes there is no change in heart rate.

Fig. 9.—Intracavitary lead from the left ventricle. One mg. of acetylcholine was injected into a jugular vein of an unanesthetized dog. Beginning and duration of the injection are denoted by the horizontal black line in the upper margin of the first strip. This is a continuous record; the last segment was taken two minutes after the injection. Note that the negative intracavitary T becomes positive during the late tachycardia.

(femoral) rather than a central artery, plus the slowness of infusion, would explain the absence of change in blood pressure and heart rate in man found by Ellis and Weiss.[20]

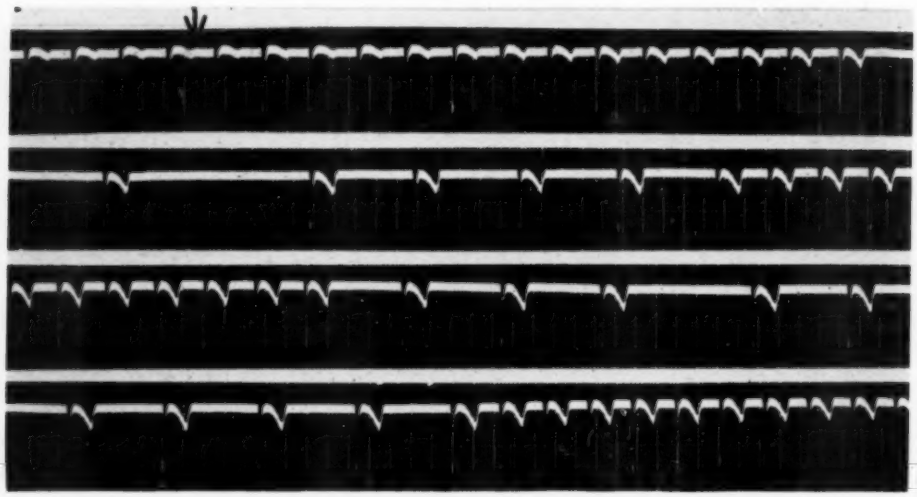

Fig. 10A.—Primary T wave changes occurring before and during the chronotropic effects produced by the injection of acetylcholine. Intracavitary lead from the left ventricle, N/20. 9.5 mg. of acetylcholine were injected into the left femoral vein. Note that the onset of primary T change (increased negativity) precedes the second degree atrioventricular block.

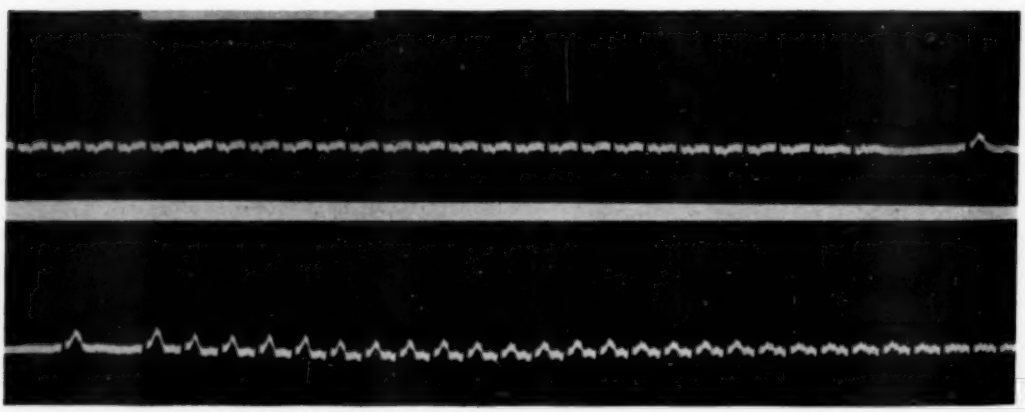

Fig. 10B.—Epicardial lead from the apex of the left ventricle, N/20. One mg. of acetylcholine was injected into the left jugular vein. Again note that the onset of the primary T change (from negative to positive) precedes the second degree atrioventricular block.

Our experiments indicate that acetylcholine alters the process of repolarization of both auricular and ventricular myocardium, resulting in primary T_a and T changes occurring independently of changes in rate. Previous experiments[14] have shown that a positive T is recorded by an intracavitary lead when the subendocardial lamina repolarizes before the subepicardial lamina; the extracavitary T is then negative. Similarly, a negative T is recorded by an intracavitary lead when the subendocardial lamina repolarizes after the subepicardial

lamina; the extracavitary T is then positive. In the present experiments acetylcholine produced a positive T wave in the extracavitary leads and an increased negativity of the intracavitary T. It is apparent, therefore, that "vagus stuff" either hastens the repolarization of the ventricular subepicardial lamina or retards it in the subendocardial lamina. That such alterations are a direct result of the acetylcholine is shown by the appearance of the changes before any fall in blood pressure and in the absence of change in heart rate. They are not due to temperature change within the cavities caused by the injection of fluid at room temperature because they did not follow control injections of normal saline.

The impulse originating in the sinoauricular node spreads radially in the atrium. There is no appreciable atrial endocardial-epicardial gradient of depolarization such as occurs in the ventricles. The topographical spread of repolarization is similar to that of depolarization.[21] The auricular T wave, unlike that of the ventricles, is therefore normally opposite in direction to the P wave. Usually, however, the auricular T is buried in the QRS complex, and T_a depression (extracavitary leads) is minimal. In our experiments the conspicuous T_a depression produced by acetylcholine was simply a marked increase of the usual negativity of the auricular T wave. On the basis of previous experiments[14] it is apparent, therefore, that acetylcholine intensifies atrial repolarization in the usual direction. In leads reflecting the negativity of the heart cavities (e.g., aV_R) the T_a elevation in association with a negative P wave (Fig. 6) is electrically indicative of the same process. In leads taken directly from the upper right auricular cavity there were several instances in which the expected T_a elevation was preceded by T_a depression (Fig. 8). We may interpret this to mean that for unknown reasons acetylcholine initially reversed the usual gradient of atrial repolarization (from upper to lower atrium) to produce a negative T_a and later intensified the usual gradient to produce a conspicuous T_a elevation. The above-described changes were reproducible and were not accompanied by a change of respiration, heart rate, or shift in position of the intracardiac electrode.

The manner in which acetylcholine produces the nonchronotropic primary T-wave changes is unknown. The possible factors include: (1) alteration in coronary flow, (2) direct myocardial action, (3) effect on vagal nerve endings in the myocardium, and (4) effect on the Purkinje meshwork.

In the dog the vagus nerve carries only vasodilator fibers for the coronary arteries,[15] and acetylcholine produces coronary vasodilatation. The resultant increase in coronary flow could hasten repolarization in a more normal fashion, from epicardium to endocardium. It may be significant that both the T-wave changes in our experiments and the increase in coronary flow in Wedd's report[5] are independent of changes in blood pressure.

The possibility of a direct action of acetylcholine upon the myocardium has been suggested by Wilburne, Schlichter, and Simon.[10] Wedd[5] has also shown that the effect of acetylcholine on the myocardium of the dog is not related to the change in coronary flow which it also produces. It seems that the entire ventricle is involved to some extent following the administration of acetylcholine. Wilburne and co-workers[10] stress the importance of the lack of ventricular escape following atrioventricular block. They conclude that acetylcholine

acts either directly on the myocardium or through vagal nerve endings, thus far undescribed, that penetrate into the ventricle in association with the Purkinje system. Cohn and Macleod,[6] however, emphasize that acetylcholine is less effective on ventricular myocardium and that such difference in action cannot be explained if acetylcholine acts directly on heart muscle. If the drug acts not on muscle itself but on vagal endings, however, they state that this selective action is understandable because it is known that vagus fibers reach nearly all parts of the atria but only the upper part of the ventricles. It seems, nevertheless, that the ventricle is appreciably affected by acetylcholine. This is demonstrated by the observations of Wilburne and co-workers and by the primary changes in the ventricular T noted in our experiments. In fact, the latter are also present in the published records of Cohn and Macleod[6] and were described by them as indicative of altered repolarization, i. e., a primary change. The importance of these primary changes in T wave was probably obscured by the associated chronotropic effects. In our experiments the change in T was more conspicuous because changes in mechanism were avoided. It is purely speculative to attribute these significant changes to action upon as yet undescribed vagal fibers in the ventricles.

Since the Purkinje system, on the other hand, is known to ramify not only subendocardially but also throughout the thickness of the ventricular walls,[17,18] making connections everywhere with myocardial fibers, the possibility must be examined that acetylcholine alters repolarization by some action on this system. Unlike depolarization, repolarization is not considered to follow the Purkinje pathways.[21] The difference in the temporal and spatial spread of the impulses of depolarization and repolarization has been thought to account for the difference in form between the QRS and T complexes. The likelihood that Purkinje fibers contain large amounts of cholinesterase[23] suggests that the transmission of impulses through these fibers is associated with the formation of acetylcholine in the network itself. Nachmansohn[24] has noted such a relationship in the conduction of a nerve impulse. The depolarized state results from a change in membrane permeability originating in the subendocardial layers, spreading centrifugally. An excess amount of exogenous acetylcholine might conceivably prolong the excited state in these deeper areas and would of necessity delay repolarization. The similarity of the effects of acetylcholine in the present experiments and of the effect of cooling of the subendocardial lamina[14] upon the epi-endocardial gradient of repolarization supports the concept of the influence of acetylcholine upon the deeper lamina by its effect on the Purkinje fibers.

SUMMARY

1. The effects of intra-arterial, intravenous, and intracardiac injection of acetylcholine upon the blood pressure and upon intracavitary and extracavitary leads of the electrocardiogram of the intact anesthetized dog were studied.

2. The intra-arterial route never resulted in early change in the electrocardiogram.

3. Minute doses were found to be effective: 0.01 μg caused fall in blood pressure; 0.1 μg caused T_a change; 5 μg resulted in change of T.

4. Acetylcholine caused very early T_a depression and increase in amplitude of the T wave in extracavitary leads. The expected reciprocal changes were seen in intracavitary leads. These changes were independent of any change in blood pressure and occurred in the absence of chronotropic effect of acetylcholine.

5. The possible mechanisms of these actions of acetylcholine are discussed.

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CRITICAL RATES IN VENTRICULAR CONDUCTION

III. Simulation of Ventricular Tachycardia

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IN PATIENTS with myocardial disease involvement of the specialized bundle branch system of the ventricles may be such that conduction is still able to be carried on normally at ordinary cardiac rates, but it fails because of fatigue when the rate is greatly increased, as during paroxysms of tachycardia.[1,2] Impairment of this conduction apparatus and paroxysms of rapid cardiac rates both occur frequently in myocardial disease, and so the coincidence of the two should not be at all uncommon. Under these circumstances bundle branch block and tachycardia are present together. Because of the short diastolic phase when the rate is very rapid, P waves in the electrocardiogram are usually merged with the preceding T wave and are not discernible. The differential diagnosis then between supraventricular tachycardia with bundle branch block and ventricular tachycardia becomes difficult, if not impossible.[3] Attention has been called to this problem and also to errors of interpretation present in some reports on the subject in the literature.[1,3,4,5] These are chiefly concerned with ventricular tachycardia and permanent bundle branch block rather than transient bundle branch block occurring above a critical cardiac rate. Mistakes have also been noted in reports on tachycardia with the syndrome of anomalous atrioventricular conduction, erroneously called ventricular tachycardia.[4] Such mistakes are not only responsible for failure to evaluate correctly the seriousness of the condition present, but they may also deprive the patient of suitable medication. Digitalis most likely would not be prescribed if the diagnosis were ventricular tachycardia, whereas in supraventricular tachycardia this may be the drug of choice.

The simulation of ventricular tachycardia by supraventricular tachycardia with bundle branch block and the role of functional fatigue block above critical cardiac rates in relation to it are described.

CASE REPORTS

Case 1.—H. F. was a 78-year-old white man admitted to the hospital for the fourth time on Feb. 6, 1950, because of increasing symptoms of cardiac failure: dyspnea, cough, and angina pectoris. He had been receiving maintenance doses of digitoxin, but because of nausea during the week before admission, the drug was not taken during that period. On examination, he appeared acutely ill; pulse was 150 per minute; respirations were 40 per minute; blood pressure was 90/72 mm. Hg. There was a double apical impulse of moderate force; dissociation was noted between

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Received for publication Aug. 7, 1950.
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the intensity of this impulse and the heart sounds, which were faint and had a tic-tac quality. Râles were heard over most of the lungs posteriorly; the liver was palpable 4 fingerbreadths below the costal margin. The diagnosis was arteriosclerotic heart disease, old myocardial infarction, aneurysm of the left ventricle, and advanced congestive heart failure.

The electrocardiogram taken on the day of admission, Feb. 6, 1950, is shown in Fig. 1,*A*. The ventricular rate was 146 per minute and regular to within 0.015 second. The P waves were not discernible. The QRS complex was aberrant, 0.20 second in duration. In Lead I it had a wide initial negative deflection of 0.09 second followed by a tall, wide (0.11 second), and notched positive wave. Though P waves could not be seen in any lead, in the right precordial lead, $CF_{1}^{6,7}$ troughs and crests were measured at a regular interval of 0.205 second, corresponding to a rate of 292, twice the ventricular rate, and suggested the presence of auricular flutter with a 2:1 block.

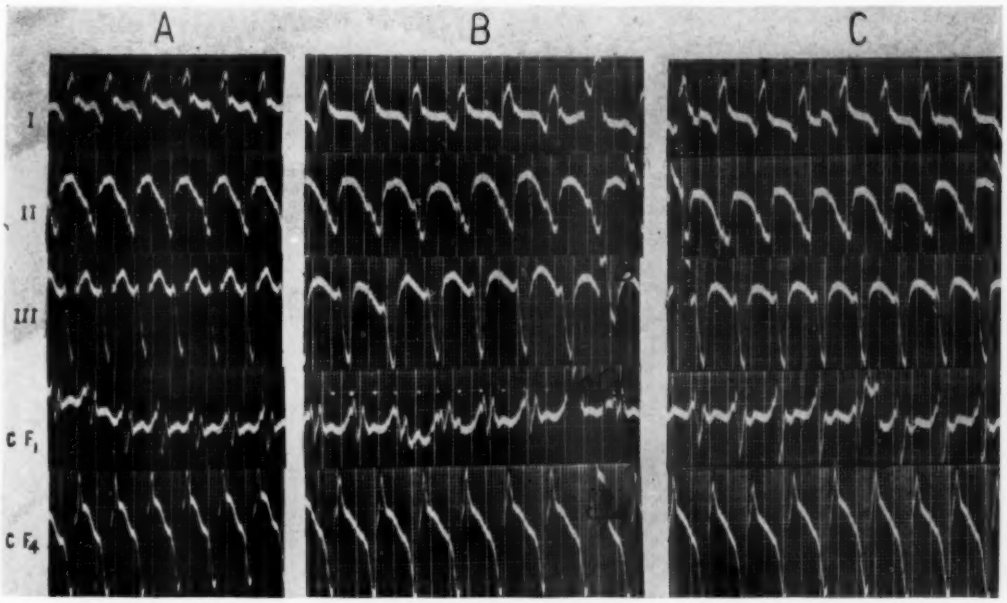

Fig. 1 (Case 1).—*A*, Feb. 6, 1950, electrocardiogram shows tachycardia, rate 146, regular; aberrant QRS complexes, 0.20 second. Suggestion of auricular flutter waves in CF_1. *B*, Feb. 7, 1950, after quinidine therapy. Rate is slower, 128 regular. Crests of flutter waves (white dots) in CF_1 are more definite; they are also seen in CF_2, shown in Fig. 1,*D*. *C*, Feb. 8, 1950. Rate is 136, regular; staircaselike flutter waves are now quite distinct in Lead CF_1, with 2:1 block.

A tracing (Fig. 1,*B*) was taken on the next day, Feb. 7, 1950, after quinidine therapy. The dose was 0.3 Gm. hourly for four doses, then every two hours for five doses; two daily doses of 0.2 mg. of digitoxin had also been given. The rate was slower but still regular at 128 per minute. The QRS complex was broader, 0.22 to 0.24 second. The intrinsicoid deflection was late in the left precordial lead CF_6, indicating late activation of the left ventricle. The R was tall with a late peak in Lead aV_L. A tall and late R′ was present in CF_1; leads farther to the right were not taken. A definite P wave was not discernible in any of the twelve leads; but, again, in CF_1, also CF_2 (Fig. 1,*D*), crests and troughs of auricular flutter waves could be measured at twice the ventricular rate. The flutter waves were more definite than in the previous tracing. The third tracing, taken on Feb. 8, 1950, about forty-eight hours after the tachycardia was first noted, is shown in Fig. 1,*C*. Quinidine medication had been continued at 0.3 Gm. every four hours. The ventricular rate was 136 per minute and regular. In CF_1 staircaselike auricular flutter waves were now quite distinct, and crests and troughs could be measured out clearly. A tracing, Fig. 1,*E*, was taken on Feb. 8, 1950, four hours after an injection of procaine amide had been given. The tachycardia had been broken, and regular sinus rhythm was present with a rate of 83 per minute. QRS was 0.08 to 0.09

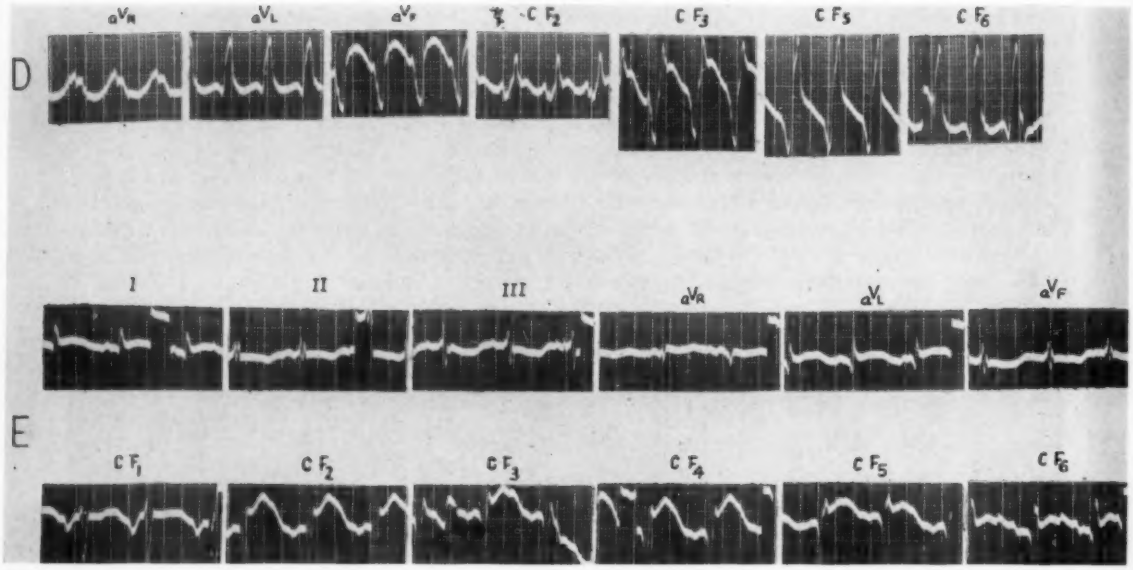

Fig. 1 (Case 1).—*D*, Part of tracing in Fig. 1,*B*. Unipolar limb leads and other precordial leads. Crests of flutter waves can be seen in CF_2. *E*, Feb. 8, 1950, later than Fig. 1,*C*. Sinus rhythm, rate 83. QRS is 0.08 to 0.09 second in duration.

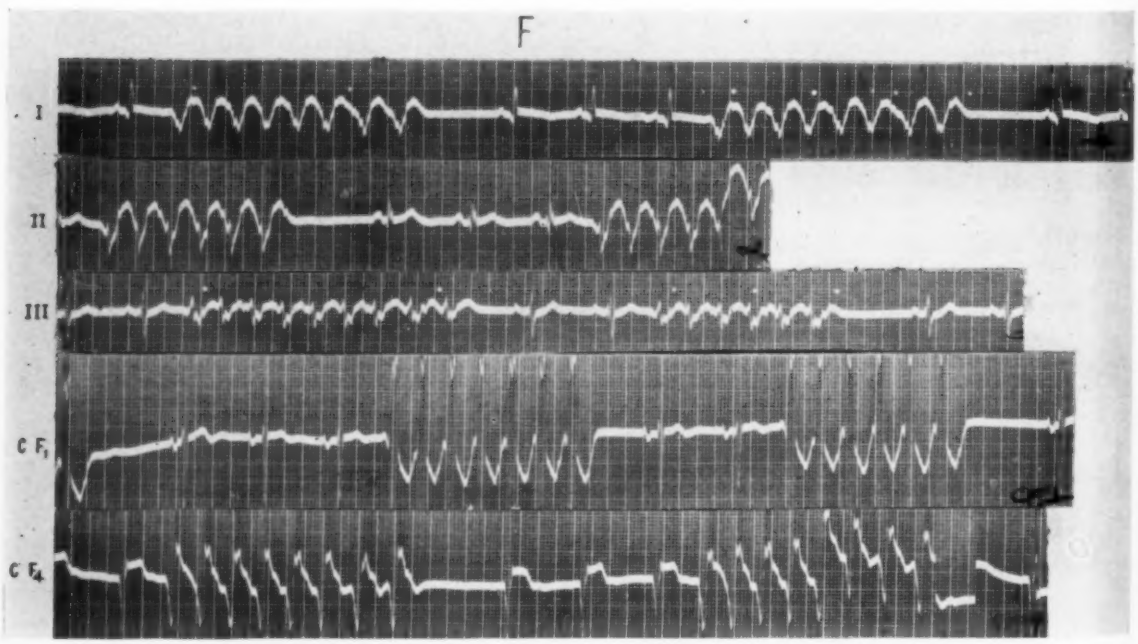

Fig. 1 (Case 1).—*F*, Feb. 18, 1950, ten paroxysms of ventricular tachycardia of 6 to 9 beats each, at a ventricular rate of 140 to 200 per minute. Each paroxysm begins with a premature ventricular contraction and ends with a compensatory pause. P waves can be seen during (white dots) and after the paroxysm at the expected time. QRS complexes are different from those seen in Fig. 1,*A*, *B*, and C.

second in duration, indicating normal conduction down both right and left main bundle branches. A tracing taken two days later was similar. Twelve days after his admission to the hospital, an episode of another arrhythmia occurred. An electrocardiogram (Fig. 1,*F*) taken at this time, Feb. 18, 1950, revealed frequent short paroxysms, 6 to 9 beats each, of true ventricular tachycardia. Each paroxysm had a typical onset with a premature ventricular contraction and ended with a compensatory pause. Evidence of P waves could be seen occurring during the paroxysm at the preparoxysmal rate and after each paroxysm at the expected time. The normal rhythm of the atria was not disturbed by the rapid ventricular beating. The ventricular rate was irregular and ranged between 140 to 200 (R-R intervals 0.30 to 0.43 second). For most of each paroxysm the rate was about 170. A striking difference from the episode of supraventricular tachycardia twelve days earlier was apparent in the rate, regularity, and configuration of the QRS complexes. For the treatment of the ventricular tachycardia, procaine amide[8] was given. There was a prompt response with cessation of the arrhythmia. The patient's condition steadily improved thereafter, and he was discharged in fairly good condition, free of cardiac failure, after seven weeks in the hospital.

The appearance of the first three electrocardiograms resembled ventricular tachycardia but on more careful analysis was seen to represent auricular flutter with bundle branch block. When the paroxysm was broken and the rate slow and below the critical rate for bundle branch block in this case, ventricular conduction appeared normal judged by the QRS of normal duration. Twelve days after the patient entered the hospital, there occurred an episode of many short paroxysms of true ventricular tachycardia. The appearance of the ventricular complexes here was very different from that in the earlier paroxysms of supraventricular tachycardia.

CASE 2.—H. R., a 60-year-old white man, was awakened from his sleep at 5 A.M. on April 18, 1948 by severe squeezing mid-chest pain. After several hours he was admitted to the hospital. On examination, he appeared acutely ill, dyspneic, and cyanotic. His temperature was 98.2° F. The heart sounds were rapid and faint, and a triple rhythm was present. A_2 was equal to P_2 and not accentuated. His blood pressure was 130/104 mm. Hg. Râles were heard at both lung bases. The liver was palpable 2 fingerbreadths below the costal margin; there was no edema. Examination of the urine revealed 2 plus sugar; the erythrocyte sedimentation rate was 22 mm. in one hour; blood nonprotein nitrogen was 43 mg. per cent. The venous pressure in an antecubital vein by direct measurement was 148 mm. of water; it rose to 210 mm. on pressure over the liver. Total circulation time with calcium gluconate was 29.5 seconds. Roentgenograms revealed extensive infiltrations scattered throughout the right lung and in the left upper lobe. There was marked generalized enlargement of the heart. The diagnosis was arteriosclerotic heart disease, myocardial infarction, congestive heart failure, and pneumonia. The therapy included oxygen by tent, quinidine, digitoxin, Mercuhydrin, aminophylline, and penicillin. The patient failed to respond to treatment. Signs of intestinal obstruction and shock developed, and on the ninth day he died.

An electrocardiogram taken on April 21, 1948 (Fig. 2,*A*) revealed the presence of auricular fibrillation with a rapid and irregular ventricular rate, about 170 per minute. The rate varied considerably; R-R intervals ranged from 0.23 to 0.54 second, corresponding to rates of 261 to 111 per minute. The QRS complex also varied considerably in size, shape, and duration in each lead. The duration varied from 0.08 to 0.14 second. There were many transitional complexes and often a series of gradual changes starting from normal. In nearly all of the aberrant QRS complexes in all leads, the configuration during the initial 0.06 to 0.07 second could be seen to be the same as in the complexes of normal duration. When there was only a small degree of block, the whole QRS complex closely resembled the normal. The duration of each QRS was closely related to the length of the preceding diastole. This was seen best in Leads II and III. In general, and making allowance for fibrillation waves, for R-R intervals of 0.50 second to 0.34 second (120 to 176 beats per minute), the duration of QRS was about 0.08 to 0.09 second; for R-R intervals of 0.33 to 0.28 second (182 to 214 per minute), the duration of QRS was about 0.10 to 0.11 second; for R-R intervals of 0. 28 to 0.26 second (214 to 230 per minute), the duration of QRS was about 0.11 to 0.13 second; and for R-R intervals of 0.26 to 0.23 second (230 to 261 per minute), the duration of QRS was about 0.12 to 0.14 second. An electrocardiogram taken later the same day, April 21, 1948 (Fig. 2,B), showed similar findings. In Lead III, for R-R intervals of 0.38 to 0.49 second (122 to 158 per minute), the duration of QRS was about 0.08 to 0.10 second.

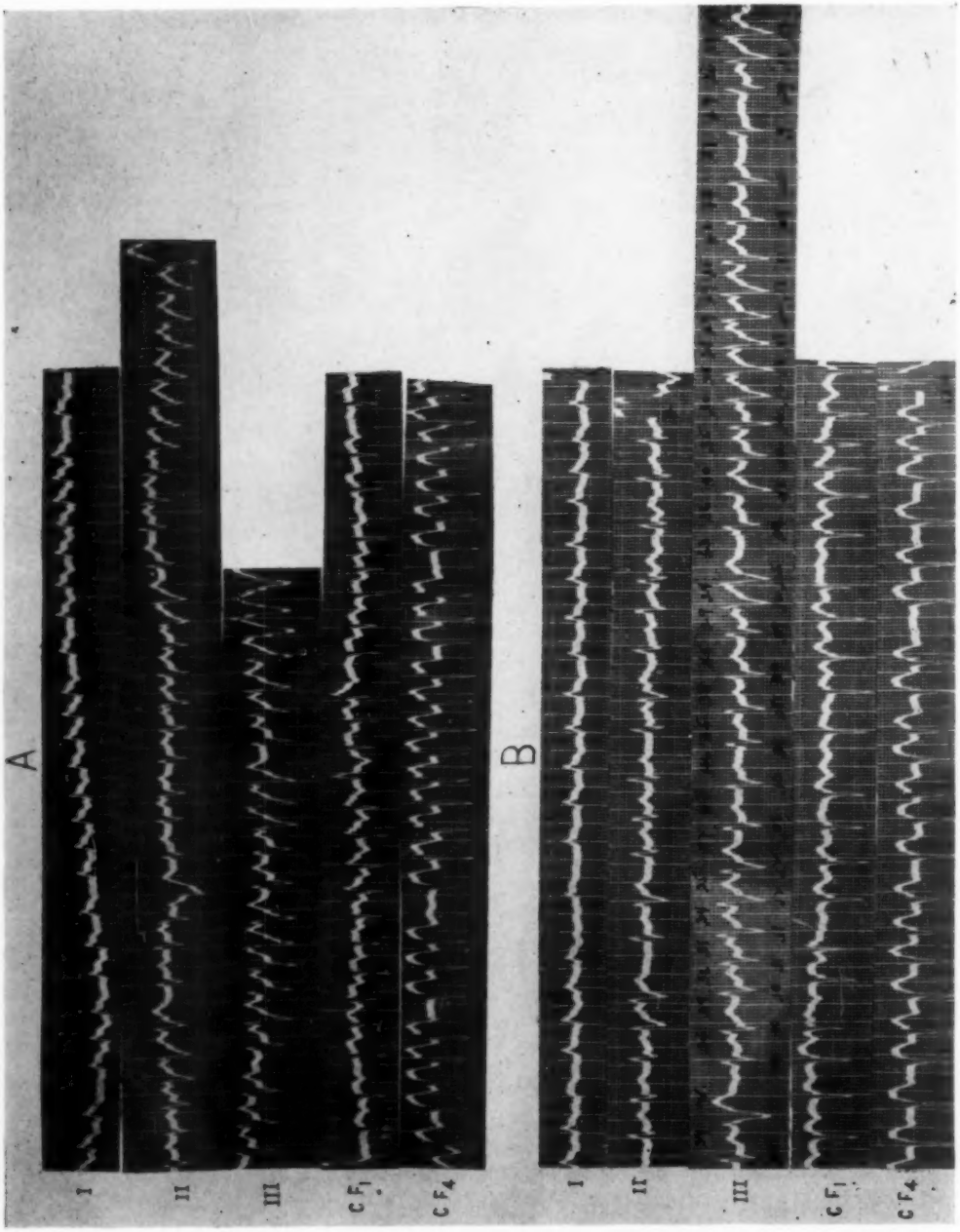

Fig. 2 (Case 2).—*A*. Electrocardiogram taken on April 21, 1948. Auricular fibrillation with a rapid and irregular ventricular rate, 111 to 261. There are many aberrant QRS complexes which in general vary in duration inversely with the preceding diastolic period. There are many transitional complexes between the normal and most aberrant ones. An ectopic ventricular beat (*V*) is seen in CF_1. In Leads II and III numbers on the upper part of the tracing are R-R intervals; numbers on the lower part are QRS durations. *B*. This record was taken later the same day and is similar to *A*. An ectopic ventricular beat (*V*) is seen in Lead III. In Lead III numbers on the upper part of the tracing are R-R intervals; numbers on the lower part are QRS durations.

For R-R intervals of 0.30 to 0.36 second (166 to 200 per minute), the QRS duration was 0.11 to 0.12 second, and for R-R intervals of 0.24 to 0.30 second (200 to 250 per minute), the QRS was 0.12 to 0.13 second. A striking feature in both tracings was the presence of transitional QRS complexes ranging from those of normal duration and appearance, supraventricular in origin, to the most aberrant complexes, 0.14 second, apparently due to complete bundle branch block, with the variations corresponding almost precisely to ventricular rate. This suggested a development of partial bundle branch block, similar to the Wenckebach type of auriculoventricular block. It differed from the usual occurrence of bundle branch block due to functional fatigue, where the complete transition from the normal QRS complex to one of complete bundle branch block takes place suddenly within the period of one cycle; this may be brought about by a change in rate of as little as one beat per minute when the heart is beating at a critical rate.[2] During parts of the tracing when the rate was most rapid, when increases in rate were more sudden, and the ventricular complexes most aberrant, the tracing could easily be taken to represent ventricular tachycardia. In the electrocardiogram (Fig. 2,*C*) taken at 8 P.M. that night (April 21, 1948) following quinidine medication, the fibrillation of the atria had stopped, and normal sinus rhythm was present with an auricular and ventricular rate of 91 per minute. The QRS complex was 0.08 second and so indicated the presence of apparently normal conduction down both main bundle branches.

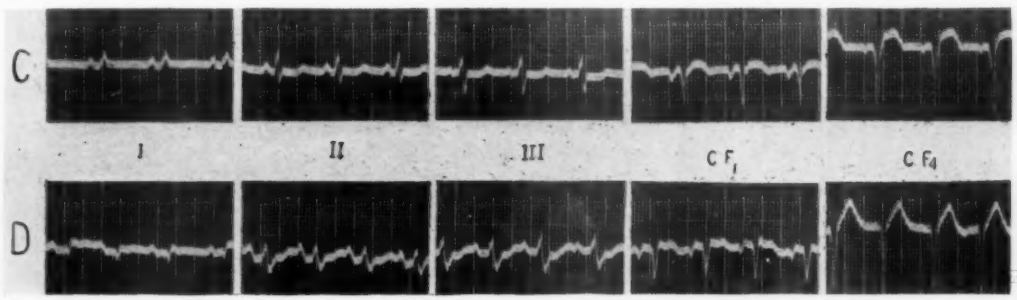

Fig. 2 (Case 2).—*C*, Record taken night of April 21, 1948, following quindine medication. Normal sinus rhythm, rate 91. QRS is 0.08 second. *D*, Record taken April 27, 1948. Sinus rhythm with rate of 110 per minute. QRS is again aberrant and resembles aberrant QRS of Fig. 2,*A* and *B*.

A tracing taken six days later, April 27, 1948 (Fig. 2,*D*), revealed sinus rhythm with an auricular and ventricular rate of about 110 per minute. The QRS complex here was more than 0.12 second, indicating bundle branch block. There was a close resemblance of the QRS to those in the earlier tracings with tachycardia. This helped to establish the interpretation of bundle branch block for the earlier tracings. Since there was good ventricular conduction with a rate of 91 and bundle branch block with a rate of 110, it would appear that the critical rate for ventricular conduction then was between these two rates, or permanent bundle branch block had ensued.

In summary, at the onset of acute myocardial infarction, auricular fibrillation developed with a rapid ventricular rate of 150 to 200 per minute. At the more rapid rates, due to functional fatigue, there was impairment of conduction down the right bundle branch. The electrocardiogram in places resembled that of paroxysmal ventricular tachycardia. At times complexes of complete bundle branch block developed gradually, after many transitional ones similar to the Wenckebach type of auriculoventricular block. Several hours later, when sinus rhythm returned and the cardiac rate was only 91, apparently normal ventricular conduction was present. Six days later, when the rate increased to 110 with sinus rhythm, bundle branch block was present again, and the QRS resembled the aberrant QRS complexes seen in the earlier tracings, Fig. 2,*A* and *B*. The critical rate for proper ventricular conduction appeared to be between 91 and 110 per minute.

CASE 3.—M. P., a 60-year-old white man, was admitted to the hospital with the complaints of cough, hemoptysis, and loss of weight over a period of a month and a half. On examination, he did not appear acutely ill; his temperature was 99.4° F., pulse 90, respirations 20 per minute. The heart was not enlarged; a systolic murmur was heard at the apex; the blood pressure was

150/70 mm. Hg. There was slight anemia and slight leucocytosis. The erythrocyte sedimentation rate was 14 mm. in one hour. Roentgenograms revealed a left âpramediastinal mass. Bronchoscopy was performed, and examination of a specimen removed showed cells suspicious of carcinoma of the lung. Pneumonectomy was advised and carried out on May 19, 1948. The postoperative course was satisfactory. The patient was able to be discharged after one week. Examination of the lobe of the lung removed revealed a large cell carcinoma of the lung. An electrocardiogram (Fig. 3,*A*) taken on May 17, 1948, two days before operation, revealed a regular sinus rhythm with an auricular and ventricular rate of 83 beats per minute. The P-R interval was 0.13 second, and the QRS complex was 0.11 second. The intrinsicoid deflection was late in leads from the right side of the precordium. Four days later, two days after operation, a tachycardia developed at a rate of about 170 per minute (Fig. 3,*B*). The rhythm was irregular. The P waves were not visible, and the QRS complex was aberrant. The appearance of the electrocardiogram resembled that of ventricular tachycardia. However, the close similarity of the QRS complex to that in the previous tracing where sinus rhythm was present rather supported the interpretation of auricular fibrillation with a rapid ventricular rate and bundle branch block.

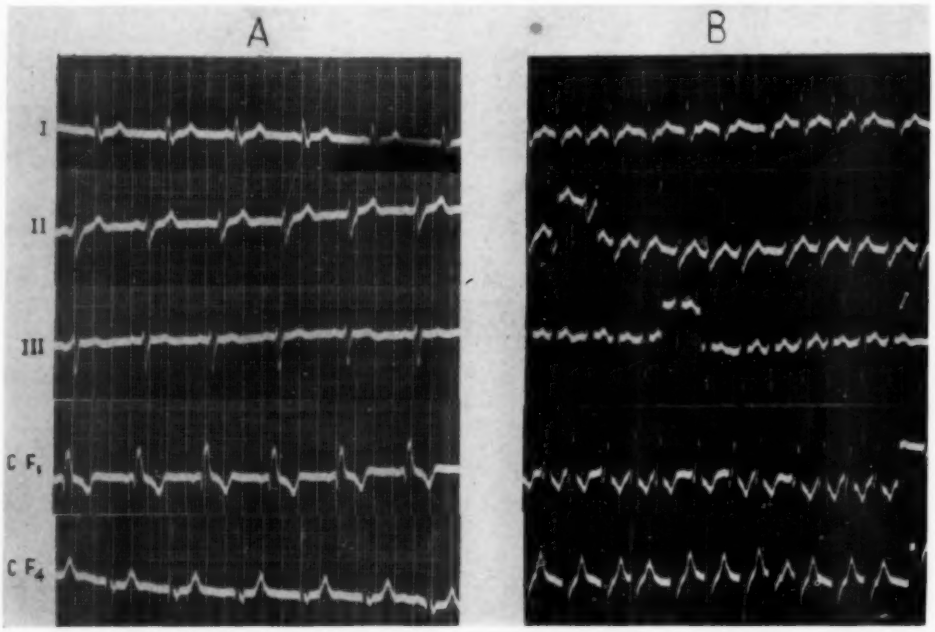

Fig. 3 (Case 3).—*A*, This record was taken on May 17, 1948, two days before operation. There is a regular sinus rhythm and wide QRS waves with a late intrinsicoid deflection in the right precordial lead CF_1, indicating the presence of right bundle branch block. *B* was taken May 21, 1948. There is auricular fibrillation and bundle branch block in places resembling ventricular tachycardia. However, the aberrant QRS complexes are similar to the ones in *A*, thus helping to establish the diagnosis of bundle branch block.

Case 4.—A. S., a 63-year-old tailor, was first admitted to the hospital on July 25, 1940, because of gall bladder disease with colic. On physical examination, the heart was normal; blood pressure was 118/86 mm. Hg. Three electrocardiograms were normal. X-ray examination revealed a moderate size hiatus hernia. The gall bladder failed to fill with dye. After two and a half weeks he was discharged. The pain, however, recurred with jaundice, and he was readmitted on Aug. 24, 1940. A cholecystectomy was performed. The gall bladder showed subacute cholecystitis and contained small calculi. In the postoperative period there occurred transient auricular fibrillation; the QRS and T deflections otherwise were normal and similar to those in the electrocardiograms of the first admission. Tests for sugar in the urine were positive, and a glucose toler-

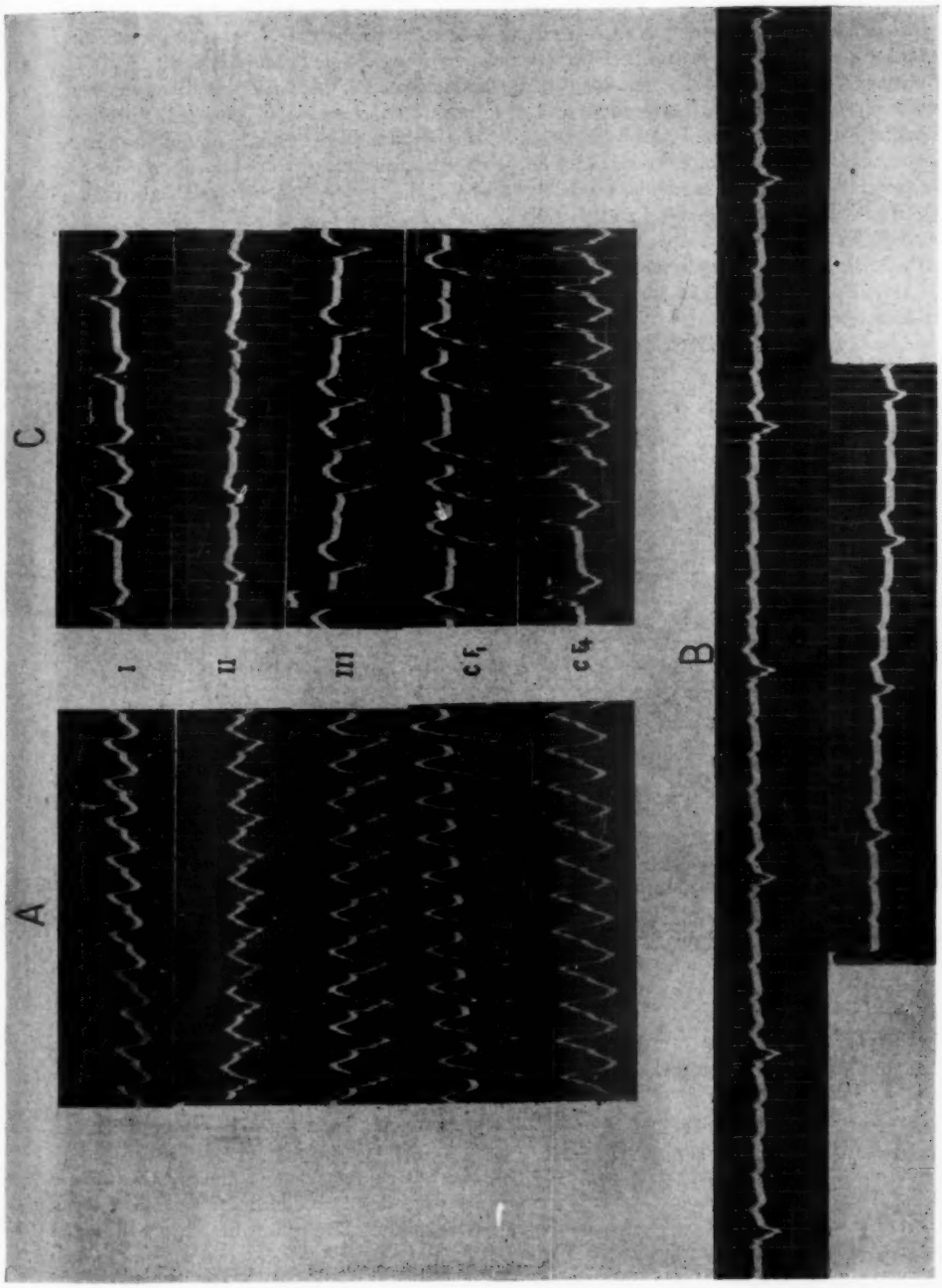

Fig. 4 (Case 4).—*A*, Record taken June 3, 1948. Tachycardia; rate 146 to 150 and regular. P waves are not visible. Duration of QRS complex was 0.16 second. *B*, Taken 20 minutes after *A*. Lead II: P waves occur regularly at a rate of 146 to 150 per minute. The ventricular rate was slow, 22 to 39 per minute. There was 4:1 to 7:1 atrioventricular block, in part resembling complete atrioventricular block. *C*, Record was taken the next day. The auricular rate was 146 per minute. There was an irregular block with periods of 2:1 block as seen in Lead II. QRS was aberrant and similar to complexes in Fig. 4.*A* and *B*.

ance test gave a diabetic curve. His third and final admission was eight years later on June 3, 1948. This was for an attack of coronary occlusion and myocardial infarction. The patient died suddenly the second day after admission.

An electrocardiogram (Fig. 4,*A*) taken June 3, 1948, revealed the presence of tachycardia with markedly aberrant QRS complexes at a rate of 146 to 150 per minute. The duration of the QRS complex was about 0.16 second. The P waves were not visible. The appearance of the tracing strongly suggested the diagnosis of ventricular tachycardia. Against this, however, was the absence of visible P waves, independent and dissociated from ventricular complexes, a salient feature in the diagnosis of ventricular tachycardia. The rhythm was regular. Against an interpretation of supraventricular tachycardia with left bundle branch block was the absence of visible P waves associated with the ventricular complexes and also the presence of the marked aberration of the QRS waves, especially seen in Leads I, III, and CF_4, strong evidence in favor of ventricular tachycardia. Twenty minutes after the tracing was completed, a recording of Lead II was repeated, Fig. 4,*B*. P waves were clearly visible at a rate of 146 to 150 per minute, the same as the previous ventricular rate seen in Fig. 4,*A* with similar QRS complexes. The ventricular rate

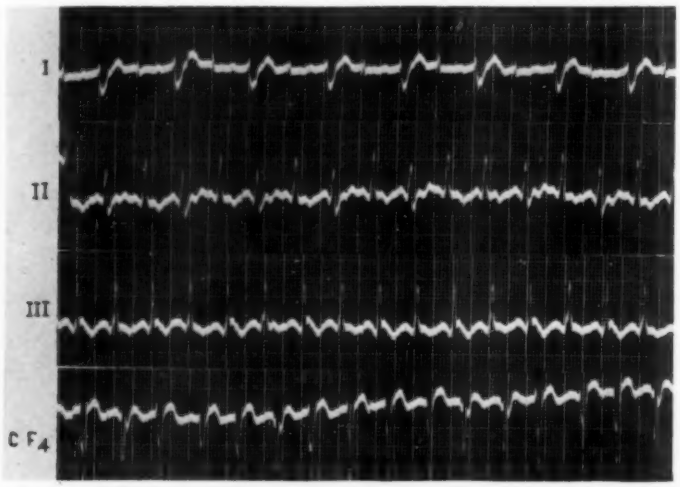

Fig. 5 (Case 5).—Record shows a ventricular rate of 150 per minute with alternate complexes aberrant. The intervals between QRS waves are equal for the two types of complexes. Crests and troughs of auricular flutter waves can be seen clearly in Lead III, occurring at a rate of 300 per minute.

now became very slow and variable, ranging from 39 to 22 per minute, a 4:1 to 7:1 atrioventricular block, in part resembling complete atrioventricular block. The next day another electrocardiogram was taken (Fig. 4,*C*). There was a rapid auricular rate about 146 per minute with rather irregular atrioventricular block but with periods of 2:1 atrioventricular block, as seen in Lead II. The P waves were of the same rate and configuration as those in Fig. 4,*B*. The QRS complexes were aberrant, 0.15 to 0.16 second, and resembled those of the previous tracings. Each was preceded by a P wave with a P-R interval of 0.26 second in Lead II, and many were in the other leads. In Lead CF_4 there was a short paroxysm of tachycardia consisting of seven ventricular beats at a rate of about 144 per minute. The rate of this paroxysm of rapid ventricular beats was the same as the ventricular rate in Fig. 4,*A* and also the same as the auricular rate in Fig. 4,*B* and *C*. The first electrocardiogram closely resembled that of ventricular tachycardia. Later tracings, however, revealed series of independent P waves at the same rapid rate, and still later ones showed the association of a P wave with the QRS wave, preceding it by a regular interval. The QRS was similar to those of the first tracing. All these features seemed to establish the diagnosis of bundle branch block for both the electrocardiograms, Fig. 4,*A* and C.

CASE 5.—S. S. was a 65-year-old man with arteriosclerotic heart disease and angina pectoris. In 1946, he developed angina of effort and one year later suffered an attack of acute coronary

occlusion and myocardial infarction for which he was hospitalized. The attack was a severe one. It was accompanied by shock and congestive heart failure. The respirations were 30 per minute; pulse rate was 92. The heart was enlarged; the heart sounds were faint; râles were present at both lung bases; the blood pressure was 96/76 mm. Hg. The erythrocyte sedimentation rate was 90 mm. in one hour. The electrocardiogram revealed changes of acute anterior wall myocardial infarction. Treatment included oxygen by tent, Mercuhydrin, and anticoagulants. He remained in the hospital forty-four days. The angina of effort continued after his discharge, and so he attended the cardiac clinic in December, 1947, and again on May 16, 1948, when the electrocardiogram in Fig. 5 was taken. There was a tachycardia with a ventricular rate of about 150 per minute. Alternate ventricular complexes were aberrant. This was seen well in Lead I. In Lead III troughs and crests of auricular flutter waves were made out, corresponding to a rate of 300 per minute with a 2:1 block. The aberrant complexes showed a wide S in Lead I, typical of right bundle branch block. The block, occurring with every other beat, suggested a factor of fatigue at the cardiac rate of 150, sufficient only to cause bundle branch block with every other beat and also to allow recovery of conduction for alternate beats. This is a condition of functional fatigue block that can be related to a critical cardiac rate. Records with 2:1 bundle branch block have been reported by Leinbach and White[9] and also by Boyer.[10] Cardiac rate and fatigue were considered possible factors.

SUMMARY AND CONCLUSIONS

The phenomenon of functional fatigue block in cardiac conduction is seen in the effect of tachycardia on conduction in the bundle branch system. Here, often in patients with myocardial disease, when critical cardiac rates are exceeded, the conduction down a bundle branch may fail. When the rate is rapid, ventricular tachycardia may be simulated. The problem of differential diagnosis was discussed as it presented itself in five cases.

In Case 1 there was a continuous tachycardia with aberrant ventricular beats, simulating ventricular tachycardia. The presence of auricular flutter with 2:1 block was revealed by the right precordial lead, especially after the rate was slowed somewhat by quinidine. Twelve days later short paroxysms of true ventricular tachycardia did occur, however, with entirely different appearing complexes. When there was sinus rhythm with a slow ventricular rate, QRS duration was within normal range, indicating the presence of conduction down the main bundle branches. The critical rate for fatigue block here was somewhere between 83 and 128 per minute.

In Case 2, with increasingly rapid rates the development of fatigue block in a bundle branch was not sudden as usual, but incomplete and gradual over a considerable range of rate increase until complete block ensued, a phenomenon similar to that seen in the Wenckebach type of atrioventricular block. In parts of the tracing when the more rapid rate continued for many beats, ventricular tachycardia was simulated. It has been stated that paroxysms of tachycardia occurring with auricular fibrillation are ventricular in origin.[11] This has been denied.[12,13] In our case, the increase in ventricular rate was often gradual and not sudden or truly paroxysmal. The interpretation of auricular fibrillation with bundle branch block in our case seemed corroborated when an electrocardiogram taken later showed sinus rhythm and bundle branch block with similar aberrant QRS complexes.

In Case 3 the possible interpretation of ventricular tachycardia was prevented by the finding of similar aberrant QRS complexes in a previous tracing

which showed clearly a sinus rhythm with a normal rate. The correct interpretation of the electrocardiogram with the tachycardia was auricular fibrillation, rapid ventricular rate, and bundle branch block.

In Case 4 the first electrocardiogram recorded tachycardia with bizarre QRS complexes, simulating ventricular tachycardia. A later tracing, after the development of atrioventricular block, 4:1 to 7:1, revealed the interpretation to be auricular tachycardia with bundle branch block. This was again confirmed still later when 2:1 atrioventricular block with a ventricular rate of 73 and a P-R interval of 0.26 second occurred regularly.

In Case 5 the phenomenon of fatigue block was seen to occur only with alternate beats when the rate was 150. At a still faster rate all the complexes might be aberrant on a basis of functional fatigue and ventricular tachycardia simulated.

Functional fatigue block in a bundle branch may occur when a critical cardiac rate is exceeded. The transition is usually sudden in one beat but uncommonly may be gradual, as in the Wenckebach type of partial atrioventricular block. When the transition occurs with paroxysmal supraventricular tachycardia, the condition of ventricular tachycardia may then be simulated. Several variations of the problem of differentiation of the two rhythms and the role of critical cardiac rates in ventricular conduction were described.

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COUPLED EXTRASYSTOLES AND AUTOMATIC VENTRICULAR RHYTHMS

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WHEN the basic dominant rhythm of the heart is disturbed by ectopic beats, two main types of such ectopic arrhythmias can be distinguished. The first, common in clinical practice, is that type in which ectopic beats follow preceding beats of the dominant rhythm at a constant time interval, that is, the beats are accurately coupled. The second, rarer than the first, is that type in which the coupling of the ectopic beats varies. In the first variety, to which alone the term extrasystoles should, in our opinion, be applied, one must assume that the ectopic beats are precipitated by the preceding one, whereas in the latter type the ectopic beats are automatic ones, due to an independent activity of the ectopic center of impulse formation.

The arrhythmias resulting from the coexistence of two independent centers of impulse formation were first studied on an extensive scale by Kaufmann and Rothberger. At one time these authors attempted to explain all instances of ectopic arrhythmias by assuming that an independent activity of two centers, termed parasystole, was the underlying mechanism,[3] and under the influence of their work other investigators also abandoned the distinction between extrasystolic and automatic mechanisms of ectopic impulse formation. Thus, in the third edition of his well-known monograph, Lewis[5] stated that, as a result of Kaufmann and Rothberger's papers, he was "unable to rewrite with sufficient confidence those distinctions between *homogenetic* and *heterogenetic* impulses which I emphasized in the last edition of this book."

Results of subsequent investigations tended to reverse this trend, and we became convinced that the separation of extrasystolic from automatic impulse formation was justified and important. On the one hand, we doubted the validity of Kaufmann and Rothberger's argument that the constant coupling of extrasystoles was due to the fact that the rates of impulse formation of the dominant and of the ectopic rhythms stood in certain simple mathematical relations to one another and pointed out that this apparent relationship is the result, and not the cause, of the constant coupling.[8] Moreover, experimental studies on the origin of extrasystoles and ectopic rhythms[9] convinced us that the ectopic beat with constant coupling is precipitated by the preceding beat which activates the ectopic impulse formation in a circumscribed focus. No author has yet succeeded in proving that extrasystoles with constant coupling are due to the independent activity of an ectopic focus.

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Received for publication May 15, 1950.

The relationship between these two forms of ectopic beats is still far from clear, and it is as a contribution to this aspect that we feel justified in reporting three unusual cases in which extrasystoles occurred exclusively after automatic idioventricular beats.

CASE REPORTS

CASE 1.—The patient, O. C., was a 70-year-old man who, in 1949, was admitted to the hospital for the third time within one year for treatment of congestive heart failure due to coronary sclerosis. Examination revealed a moderately enlarged left ventricle, a loud aortic systolic murmur, and auricular fibrillation. The blood pressure was about 200/95 mm. Hg. The patient also had mild diabetes for which he was given daily 7 units each of soluble and of protamine zinc insulin. As a result of digitalis, his cardiac status improved. The record reproduced in Fig. 1 was obtained while he was receiving 0.25 mg. of digoxin twice daily. The same kind of arrhythmia was again recorded two days later when the patient was discharged.

The electrocardiogram (Fig. 1) showed auricular fibrillation with a slow ventricular rate. Two different kinds of ventricular complexes and, in addition, ventricular extrasystoles were recorded. The first type of ventricular complexes, representing those due to supraventricular conducted impulses, are seen in the fifth complex in Lead I, the first four complexes in Lead II, the second, third, fourth, and seventh in Lead III, the third and fourth in Lead CF_2, and the first four complexes in Lead CF_5 showed distortion of the RS-T intervals and inversion of the T waves, due to digitalis, but no other abnormalities. The second type of ventricular complexes had widened initial deflections measuring 0.12 second; in Lead I a low R wave was followed by a deep and slurred S wave, and in Lead III a small Q wave preceded a tall R wave, the descending limb of which was slurred. In the chest leads these complexes essentially resembled those in Lead I, particularly in respect to the deep and slurred S waves. The shape of these complexes and also a slight delay of the intrinsic deflection in Lead CF_2 suggested that those beats originated in the left ventricle and activated the right ventricle after some delay. The last ventricular complex in CF_2 seemed to represent a combination between the conducted and automatic beats.

The unusual feature of this as well as of the subsequent records was the occurrence of extrasystoles exclusively following automatic idioventricular beats. It will be noticed that none of the six extrasystoles recorded in the various leads was preceded by a supraventricular conducted beat. The coupling of the extrasystoles was fairly constant (0.48 to 0.52 second).

CASE 2.—P. T., a man 85 years old, was admitted to the hospital for congestive heart failure. Examination showed emphysema of the lungs, moderate dilatation of the left ventricle, a systolic murmur over the apical and aortic regions, and auricular fibrillation. The blood pressure was about 130/80 mm. Hg. This patient was also given digitalis and had had 0.1 Gm. of the powdered leaves twice daily for a fortnight when the tracing reproduced in Fig. 2 was obtained. Again, three different kinds of ventricular complexes were seen, namely conducted supraventricular, idioventricular automatic impulses, and extrasystoles. The conducted beats (third, fourth, and seventh in Lead I, all of Lead II, first, fourth, and fifth in Lead III, none in CF_2, and first, second, third, and sixth in Lead CF_5) showed the typical features of right bundle branch block. The automatic idioventricular beats showed essentially the same features as those of Case 1. Again, extrasystoles were recorded exclusively after automatic beats (two each in Leads I, III, and CF_2, and one in Lead CF_5). The coupling of the extrasystole varied within narrow limits (0.42 to 0.48 second) with the exception of the first extrasystole in Lead CF_2 where the interval was 0.56 second. This lead also showed the varying in shape of the extrasystoles which is a common feature in patients receiving digitalis, but is observed also in patients with coronary sclerosis without digitalis. When the drug was discontinued, this arrhythmia disappeared.

CASE 3.—The clinical diagnosis in H. R., a 57-year-old woman, was rheumatic mitral stenosis and incompetence. The basic rhythm was auricular flutter changing into auricular fibrillation, and the patient was given large doses of digitalis (0.5 Gm. of powdered leaf daily) for the purpose of effecting this conversion of rhythm. Observation over a period of five days revealed throughout this time the occurrence of automatic ventricular beats in varying phases of diastole, and analysis

of longer records showed the unusual phenomenon of parasystole in a case of auricular fibrillation. In Fig. 3 some representative portions of the records, all of Lead II, are reproduced. In addition to auricular fibrillation, automatic idioventricular beats were seen which were separated by the following intervals (expressed in 0.01 second): 172 in Fig. 3,*A*; 170 in Fig. 3,*B*; 325 in Fig. 3,*C*; and 478 in Fig. 3,*D*. The variations in the rate underlying the automatic idioventricular rhythm are due to the fact that the tracings shown in Fig. 3 were obtained on different days; moreover, in parasystole with slow idioventricular rhythm variations in rate of such degree are not uncommon. The phenomenon to which we wish to draw attention is that all except one of the

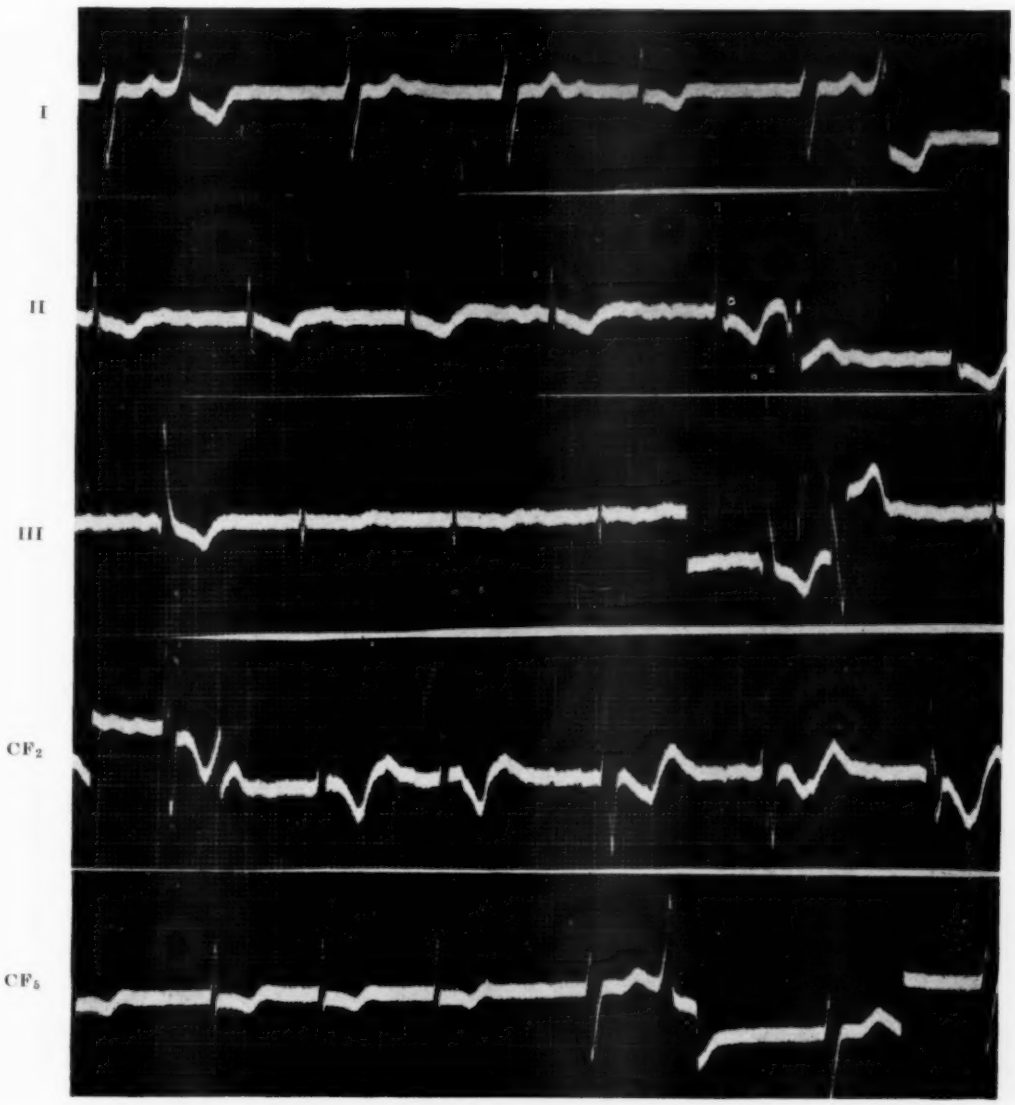

Fig. 1.—The three standard leads and Leads CF_2 and CF_5. Auricular fibrillation with conducted beats, idioventricular beats, and ventricular extrasystoles. All six ventricular extrasystoles are coupled to an idioventricular beat.

automatic beats were followed by extrasystoles having varying shapes but fairly constant coupling. Extrasystoles were never observed after conducted beats.

DISCUSSION

The unusual phenomenon common to these three cases is the occurrence of extrasystoles exclusively after automatic idioventricular beats; they were never observed after supraventricular conducted beats. The fairly constant coupling to the preceding beat of the complexes in question showed that they were, in fact, extrasystoles and were not due to supraventricular impulses with aberrant conduction in the ventricles. In all three patients auricular fibrillation

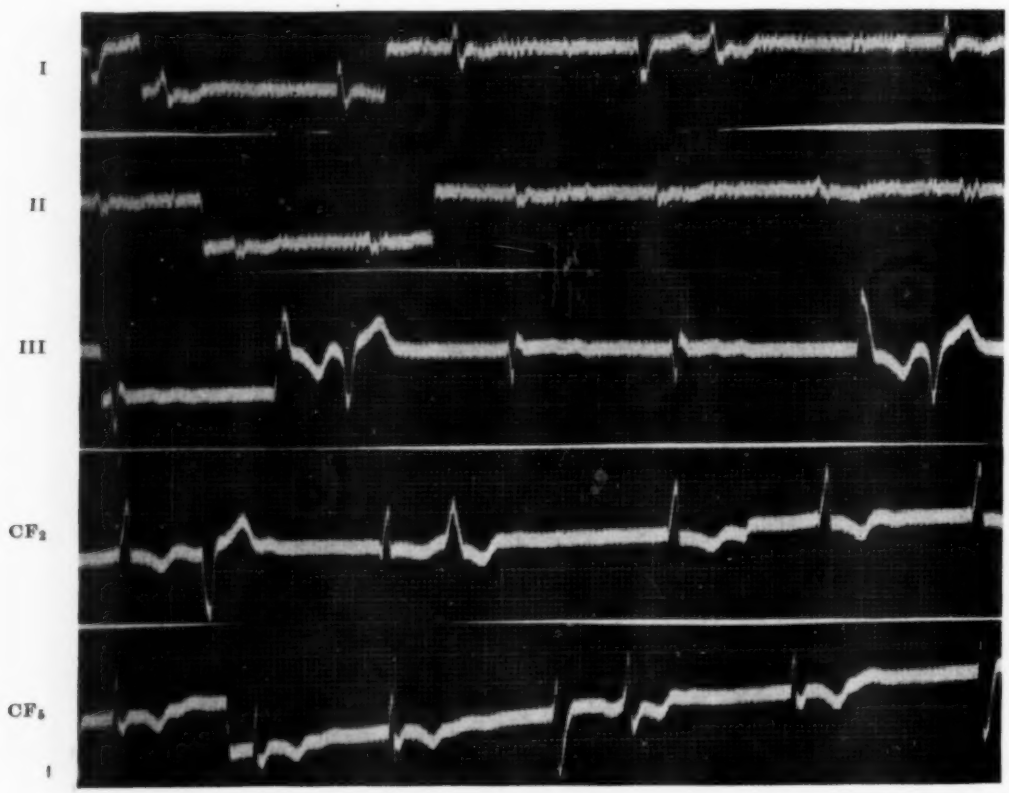

Fig. 2.—The three standard leads and Leads CF_2 and CF_5. Auricular fibrillation with conducted ventricular beats and idioventricular beats. Seven ventricular extrasystoles are bound exclusively to the idioventricular beats.

was the underlying rhythm, and all received digitalis. Large doses of this drug were given only in Case 3, but the remaining two patients were old; a greater sensitivity to digitalis and proneness to develop abnormal rhythms, particularly idioventricular rhythms, in old patients as compared with younger patients is well recognized. It would, however, be premature to conclude from the observations on this small number that this unusual arrhythmia occurs only in instances of auricular fibrillation during digitalis treatment.

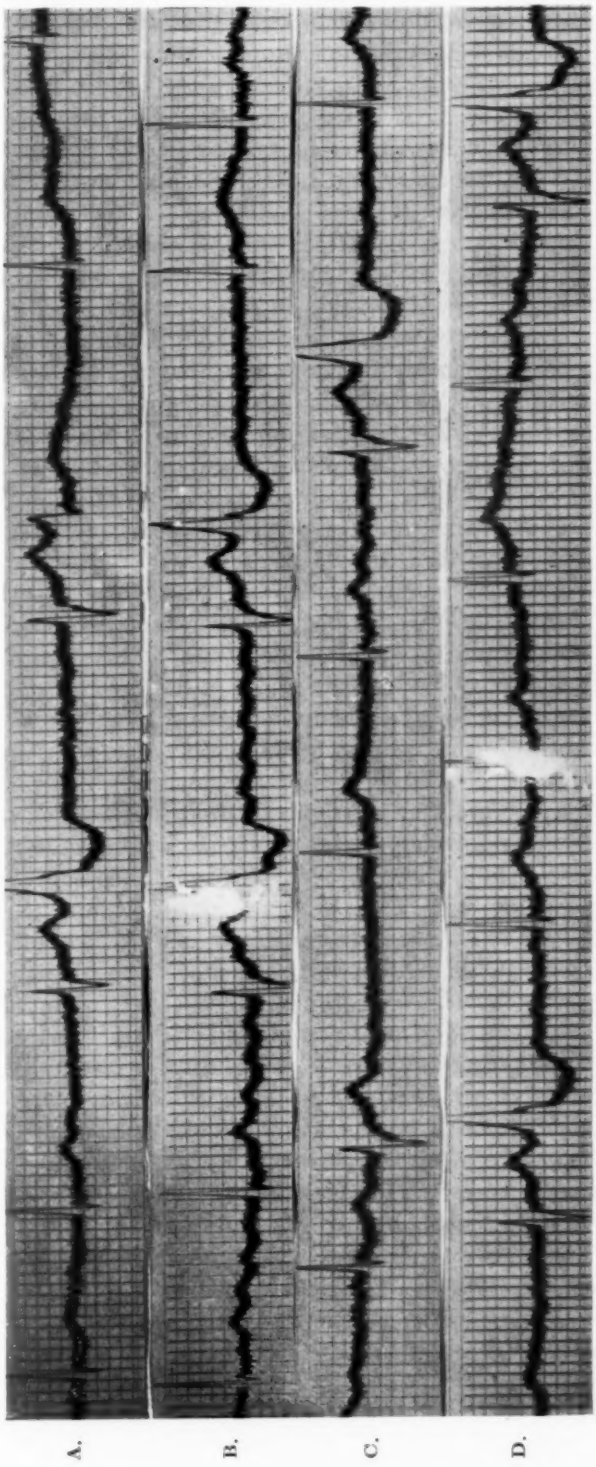

Fig. 3.—All tracings made on Lead II. Auricular fibrillation with conducted ventricular beats and parasystolic, automatic ventricular systoles. Seven extrasystoles in these tracings are all bound exclusively to automatic beats.

The relationship between automatic (parasystolic) and extrasystolic (i.e., precipitated by the preceding beat) ectopic impulse formation has been studied repeatedly. In 1930, we described a case of parasystole with simple interference, changing during digitalis treatment into bigeminal rhythm due to extrasystoles of the same appearance with constant coupling.[12] Subsequently, similar observations were published by Rothberger[7] and by Vedoya and Battini.[15] Automatic and extrasystolic beats may even originate in immediate succession in the same center.[1,6,13] If automatic and extrasystolic beats originate in the same focus, the explanation centers around the mechanism underlying, on the one hand, an independent automatic activity of the ectopic focus and, on the other hand, its activity invariably dependent on and precipitated by the preceding beat. The present observation is fundamentally different. Here, the salient point is that extrasystoles were initiated exclusively by automatic idioventricular beats. The failure of supraventricular conducted impulses to initiate extrasystoles is difficult to understand, for it was demonstrated experimentally[9] that, once an ectopic center has become active, every impulse originating in any part of the ventricle precipitates an extrasystole, providing it reaches the focus during its spread through the ventricles. If the ectopic center were situated at a distance from the one producing the automatic beats, it would be expected that the supraventricular conducted impulses would also give rise to extrasystoles in this center. If, on the other hand, it were assumed that the extrasystoles originate in the same focus which produces the automatic beats, the great difference in shape between the extrasystoles and the automatic beats, which was invariably observed, would require an explanation. This cannot easily be attributed to disturbances of conduction of the ectopic impulse, for several extrasystoles with the same coupling had different shapes and if, as in Fig. 2, Lead CF_2, extrasystoles with entirely different shapes and varying coupling were recorded, the one with the longer coupling differed in shape from the preceding automatic beat even more than the extrasystole with the shorter coupling. It is more reasonable to assume that the extrasystoles originated in a focus at a distance from the automatic center and that, for the reasons mentioned in connection with Case 2, several extrasystolic foci were sometimes active. The available data, however, do not permit one to dismiss completely the possibility that idioventricular beats and extrasystoles originate in the same center. We would be dealing with stimulus formation in groups (repetitive firing), and the second stimulus which rapidly follows the preceding one could be conducted aberrantly.

If the assumed location of the extrasystolic focus at a distance from that of the automatic beats is correct, the salient feature of the mechanism underlying this unusual arrhythmia must be a directional one. In this respect it is to some extent reminiscent of, though by no means identical with, some observations made in cases of complete atrioventricular block with retrograde conduction of the idioventricular beats to the auricles. This retrograde conduction of an impulse in the absence of conduction in the normal direction was explained by the assumption of a unidirectional block, allowing the passage of an impulse in only one direction while blocking it in the reverse one. As far as the scanty anatomical observations available in such cases[4,16,17] make it possible to form an

opinion, it seems that the site of the area of depressed conduction is reponsible for the unidirectional conduction. Unidirectional block and abnormal pathways of conduction, owing to the presence of refractory tissue, were also considered responsible for the occurrence of return extrasystoles[10,14] and Decherd and Ruskin,[2] in this connection, assumed "an area of refractory tissue of varying size and shape, and/or varying stages of recovery" near the atrioventricular node. It seems to us that, in order to explain tentatively the present observation, a reasonable assumption would be the presence of refractory tissue in the vicinity of the center or centers of extrasystolic impulse formation, affording a protective block of this center against the supraventricular impulses spreading through the ventricles from the bifurcation through normal (Cases 1 and 3) or at least partly normal (Case 2, right bundle branch block) pathways. The location of this refractory tissue (which has to be presumed) would be such that the protective block afforded to the extrasystolic center is not complete, but allows the passage to the center of impulses coming from certain directions. The spread through the ventricles of the automatic idioventricular impulses differs greatly from that of the supraventricular ones, as evidenced by the difference in shape and by the conspicuous widening of the initial deflections, and it would thus be understandable that automatic impulses, reaching the extrasystolic center from a direction entirely different from that of the supraventricular impulses, are able to reach it whereas the latter are blocked by refractory tissues.

Analysis of more tracings of these rare disturbances of rhythm will be necessary before definite conclusions regarding their mechanism are drawn.

SUMMARY

Three cases of auricular fibrillation with automatic idioventricular beats are reported in which extrasystoles followed automatic idioventricular beats exclusively, while they were never observed after conducted supraventricular beats. In Case 3 a parasystolic mechanism of the automatic rhythm could be established. In *all* cases the patient was receiving digitalis, but the number of observations is *too small* to indicate whether this kind of arrhythmia occurs only in auricular fibrillation during digitalis treatment. The relationship between extrasystolic and automatic impulse formation is briefly reviewed. While a completely satisfactory explanation of the present observation cannot be offered, the assumption of a directional protective block of the extrasystolic center, due to the presence of refractory tissue in the vicinity of the center, is put forward as a tentative explanation. The location of the refractory tissue is assumed to be such that it allows the passage to the center of impulses coming from certain directions, while impulses arriving from other directions are blocked by it. This tentative explanation is supported by similar, though not identical, assumptions made in order to explain the mechanism underlying return extrasystoles and the retrograde conduction of idioventricular impulses in cases of complete atrioventricular block; these assumptions are briefly discussed. Stimulus formation "in groups" in an idioventricular center with aberrant conduction of the second stimulus also deserves consideration.

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COR TRILOCULARE BIATRIATUM: AN ANALYSIS OF THE CLINICAL AND PATHOLOGIC FEATURES OF NINE CASES*

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ISOLATED cases are usually described in accounts of cor triloculare biatriatum, a relatively unusual condition wherein a common cardiac ventricle exists in the presence of two atria. These reports often single out patients of unusual interest. Weighting of the literature by such examples results in a restricted understanding of this condition. The present report on nine patients with cor triloculare biatriatum represents a study of all the pathologic specimens of this condition in the collection of the Mayo Clinic. It is hoped that the analysis of these cases will give a comprehensive idea as to the diversity of the pathologic and clinical features of this condition.

ANATOMIC CLASSIFICATION

In the majority of patients with cor triloculare biatriatum, the great vessels are transposed. The aorta lies anterior to the pulmonary trunk and often on a plane somewhat to the right of the latter. The two great vessels run parallel, and normal spiraling about each other is absent. We are arbitrarily designating the malformation in which transposition is present as type 1. A very unusual form of cor triloculare biatriatum is that in which the great vessels are not transposed. This type is designated as type 2.

Type 1 may be divided into four subtypes, depending on the nature of the approach to the major arteries, as follows: (A) The outflow portion of the common ventricle is subdivided to form a narrow subaortic channel (Fig. 1); (B) the outflow portion of the common ventricle is subdivided so that the result is a narrow subpulmonary channel, stenosis of the pulmonary trunk, or subpulmonary fibrous stenosis (Fig. 2); (C) the outflow portion of the common ventricle is subdivided into subaortic and subpulmonary channels of about equal diameters; and (D) the outflow portion of the common ventricle is not subdivided.

The structure of the ventricle in cor triloculare biatriatum forms an interesting and fascinating problem in the study of congenital cardiac disease. As a rule, the common ventricle is divided by a muscular ridge which extends from the posterior wall of the base of the ventricle forward and to the right

Received for publication July 19, 1950.

*Abridgment of a portion of a thesis submitted by Dr. H. Milton Rogers to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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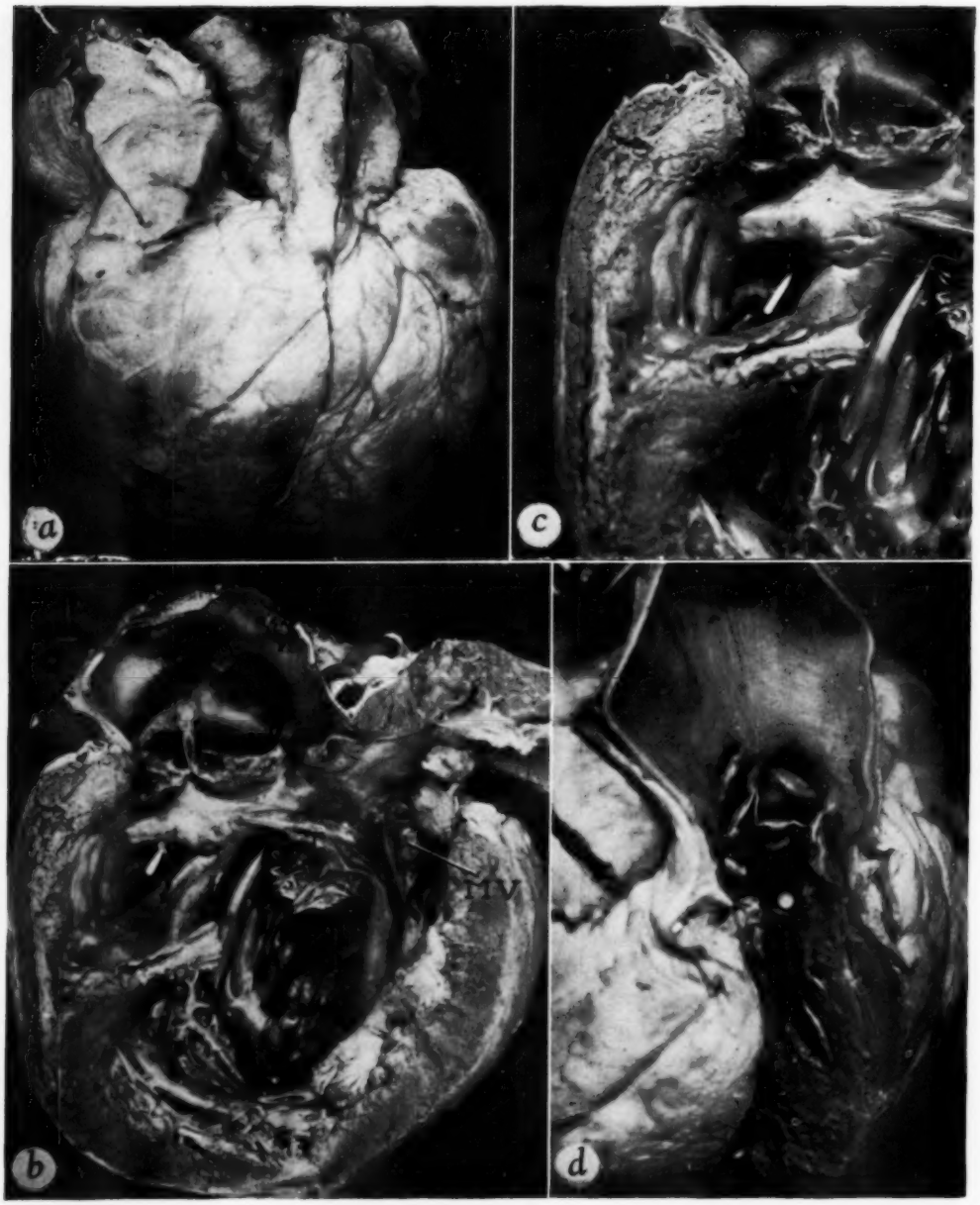

Fig. 1 (Case 8).—Cor triloculare biatriatum, type 1A. *a*, The exterior of the heart and great vessels viewed from in front. There is transposition of the great vessels. The narrow aorta lies anterior and parallel to the wide pulmonary trunk. *b*, The interior of the common ventricle and the opened pulmonary valve. The mitral (*M. V.*) and tricuspid (*T. V.*) orifices lead into the sinus of the common ventricle. The pulmonary orifice is wide. A muscular band runs between the anterior and posterior walls of the common ventricle creating a narrow subaortic pocket (containing probe). *c*, Close-up of lower end of the narrow subaortic pocket (containing probe) and opened pulmonary orifice. *d*, Aortic valve and upper end of subaortic pocket (containing probe) viewed from above.

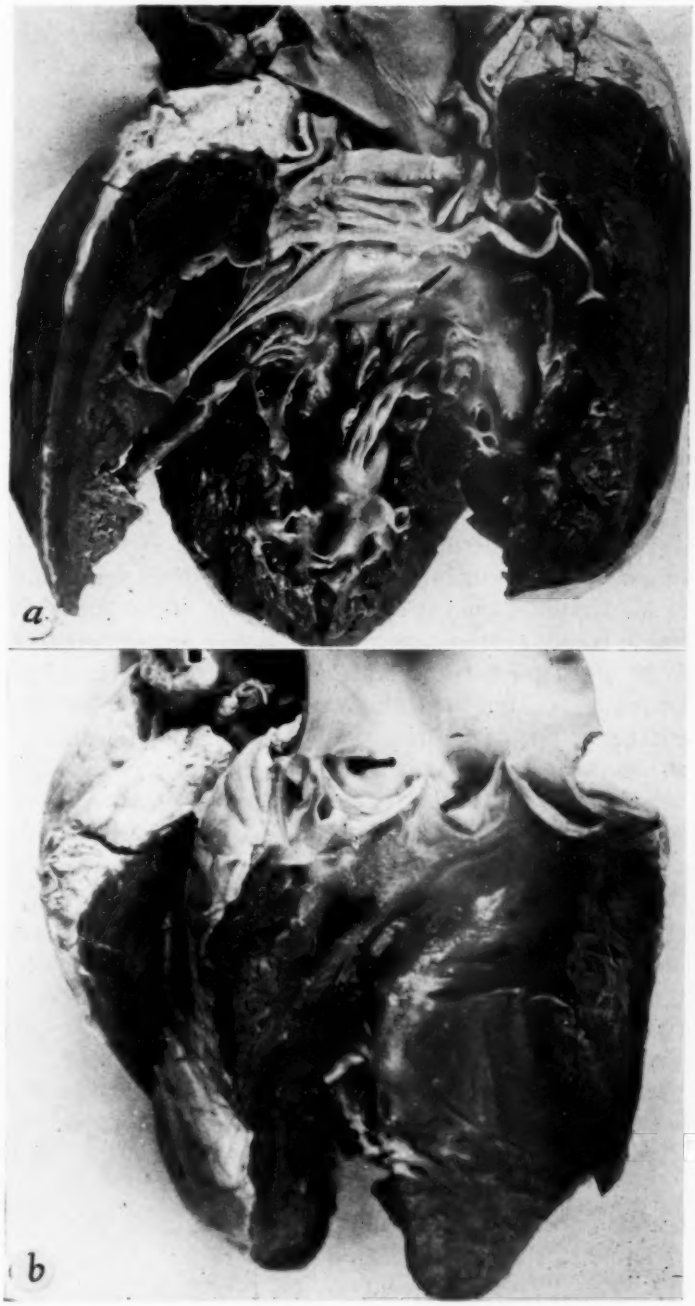

Fig. 2 (Case 2).—Cor triloculare biatriatum, type 1B. *a*, The common ventricle and the pulmonary orifice. While the pulmonary orifice is wide, there is a fibrous intrapulmonary collar producing subpulmonary stenosis. *b*, The aortic orifice and subaortic pocket. The inlet to the latter is not as narrow as that in Fig. 1 (probes in coronary arteries).

to join the anterior wall in the region of the tricuspid ring. Consequently, the outlet or conus of the single ventricle often has a large posterior subpulmonary component and a smaller subaortic component lying anteriorly. Considerable discussion has evolved as to whether or not the muscular band is ventricular septal tissue or some other tissue. If the band represents a ventricular septum, the small anterior pocket which it forms would, of necessity, have to be considered as a ventricle. If, on the other hand, the muscular band is other than septal tissue, the small pocket would not be a second ventricle but an integral part of a common ventricle.

This muscular band has the same appearance as the crista supraventricularis has in the tetralogy of Fallot wherein it separates from the right ventricular outflow tract the subpulmonary outflow channel, the so-called third ventricle. Admittedly, the so-called third ventricle is not a third chamber, but it represents part of the outflow channel of the right ventricle. The muscular band in the right ventricle in patients with the tetralogy of Fallot is considered to be the crista supraventricularis. It is our opinion that the muscular band that runs between the posterior and anterior ventricular walls of the ventricle in cor triloculare biatriatum is the same structure, namely, the crista supraventricularis. As we have this view in mind, our interpretation of the small ventricular pocket in cor triloculare biatriatum is that it represents a part of the outflow tract of the common ventricle rather than a separate ventricle. In support of this view is the fact that the small pocket does not communicate with an atrium through an atrioventricular orifice, but instead the two atrioventricular orifices communicate with the larger component of the common ventricle. In some patients with this anomaly, the crista supraventricularis is poorly developed, and, consequently, evidence of a conal pocket is absent. Such patients are not basically different in nature from those with a well-developed crista supraventricularis and a basilar pocket. The only difference is that of the degree of development of the crista supraventricularis.

Favorite[8] has attempted to divide patients with cor triloculare biatriatum into two groups, the division depending upon whether or not the conus was divided. He classified those patients in whom the outflow pocket was absent as having "true cor triloculare biatriatum" and those in whom the outflow pocket was present as having "functional cor triloculare biatriatum." This view is contrary to that of Abbott[1] who considered that the presence or absence of the outflow pocket did not in itself alter the concept as to the basic malformation. Taussig[19] likewise shared this belief. We are in support of the view of Abbott and Taussig.

The pathologic and clinical features of the nine cases being presented are summaried in Table I.

ANALYSIS OF CASES

As mentioned previously, in the vast majority of patients cor triloculare biatriatum is associated with transposition of the great vessels. This was observed in eight of our nine patients with cor triloculare biatriatum. When transposition exists, the aorta communicates with the basilar outflow pocket

of the common ventricle, if one is present. As a rule, if a basilar pocket exists, it lies toward the right but may, as in two of our patients, lie to the left. It is of interest that in one of the latter patients (Case 4) isolated dextrocardia also occurred (Fig. 3). Six of our patients belonged to type 1A, that is, the great vessels were transposed, and the outflow portion of the common ventricle was so divided as to create a narrow subaortic outflow tract in association with a wide pulmonary trunk and a wide subpulmonary portion of the outflow tract.

TABLE I. SUMMARY OF FEATURES OF 9 CONSECUTIVE CASES OF COR TRILOCULARE BIATRIATUM

CASE	SEX	AGE	PATHOLOGIC TYPE	CYANOSIS	MURMUR
1	M	10 months	1A	At birth	Loud systolic murmur over entire chest
2	M	6 years	1B	Minimal	Systolic blowing, entire precordium
3	M	2½ months	1A	Mild	?
4	F	10 months	1B	At 7 months, then progressive	Systolic murmur over right side of precordium
5	F	5 months	1A	Terminal	Systolic and rough; loudest in left second interspace
6	M	3 weeks	2	Mild	Loud blowing systolic murmur, most marked along left border of sternum
7*	F	3 weeks	1A	Moderate	Systolic murmur over precordium
8†	M	3 years	1A	Moderate	?
9‡	M	8 years	1A	Moderate	Systolic murmur, second and third left interspaces

*The clinical data and the specimen of this patient were submitted through the courtesy of Dr. Edward Cole, St. Petersburg, Fla.

†Dr. D. F. H. Murphy, Beverly, Mass., kindly submitted the specimen of this patient.

‡This patient was studied clinically by Dr. A. Carlton Ernstene, Cleveland, Ohio, and the specimen was submitted by Dr. W. B. Chamberlin, Jr., Cleveland, Ohio.

It is realized that the ventricular ejectile force which sends the blood to the lungs and to the systemic circulation is one and the same. This means that in type 1A, if systemic flow is to be adequate, pulmonary hypertension must exist. The latter factor is probably dependent upon retention by the lungs of muscular arteries with fetal characteristics. Later, occlusive intimal fibrous changes appear in the intrapulmonary arteries, creating a condition which may be termed "intrapulmonary pulmonary stenosis." In type 1A the structure of the intrapulmonary arteries simulates that in the Eisenmenger complex[3,6] and in coarctation of the aorta proximal to a patent ductus arteriosus.[7]

In two of our nine patients muscular subdivision of the outflow portion of the common ventricle did not exist, but a fibrous collar was present immediately beneath the relatively wide pulmonary orifice, which created a degree of subpulmonary stenosis. One patient was 10 months of age, the other 6 years. The microscopic picture of the pulmonary vessels of each of these patients was within normal bounds. These facts are to be interpreted as follows: The subpulmonary stenosis was of sufficient degree to allow the common ventricle

to build up enough pressure to supply the systemic circulation, and, at the same time, to spare the pulmonary vessels from the responsibility of regulating the distribution of the blood leaving the common ventricle. In these patients the pulmonary blood pressure was probably within normal limits. The normality of the pulmonary vessels and their dynamics are comparable to those associated with stenosis of ostium infundibuli.[3]

The fact that cor triloculare biatriatum without transposition of the great vessels is exceedingly rare was emphasized by Drey, Strauss, and Gray.[4] They reported one such case. In this patient the pulmonary trunk arose from a basilar ventricular outflow pocket. They stated that only one other case similar to theirs, namely, that described by Holmes,[13] had ever been reported. One of our cases (Case 6) is pertinent in a discussion of this type because the great vessels were not transposed (Fig. 4). It differs from the case reported by Drey, Strauss,

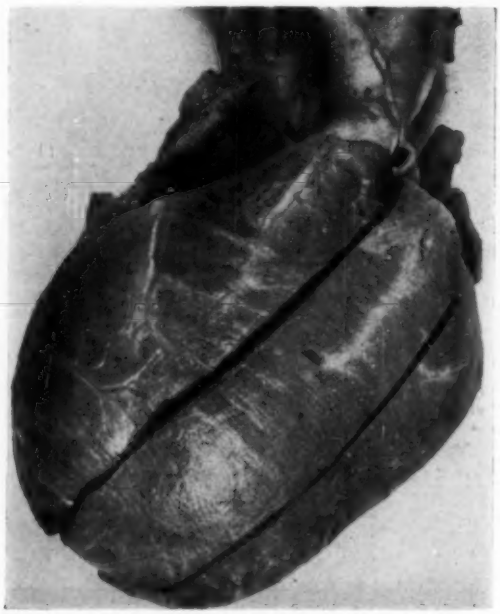

Fig. 3 (Case 4).—Cor triloculare biatriatum with isolated dextrocardia. The apex is to the right. The aorta lies in a transposed position.

and Gray and the one reported by Holmes in that the crista supraventricularis was not well developed and a separate outflow tract did not exist in the common ventricle. One other difference is that our patient had a common atrioventricular orifice, while in the cases reported by Drey, Strauss, and Gray and by Holmes the patients had tricuspid and mitral orifices.

Tubular hypoplasia of the aortic arch occurred in two of our patients (Cases 5 and 7) (Fig. 5). In each instance, the change was restricted to that portion of the arch between the origins of the left common carotid and left subclavian arteries, and the ductus arteriosus was patent. In one patient (Case 5) coarctation of the aorta also occurred just proximal to a narrowly patent ductus arteriosus. Coarctation of the aorta proximal to a closed ductus arteriosus was present in the 3-year-old patient (Case 8).

Five patients had patent ductus arteriosus (Cases 1, 3, 5, 6, and 7), and their ages were 10 months, 2½ months, 5 months, 3 weeks, and 3 weeks, respectively. Patency was minimal in the two older patients.

Bicuspid pulmonary valves were present in two patients (Cases 1 and 4), and bicuspid aortic valves occurred in two patients (Cases 6 and 7).

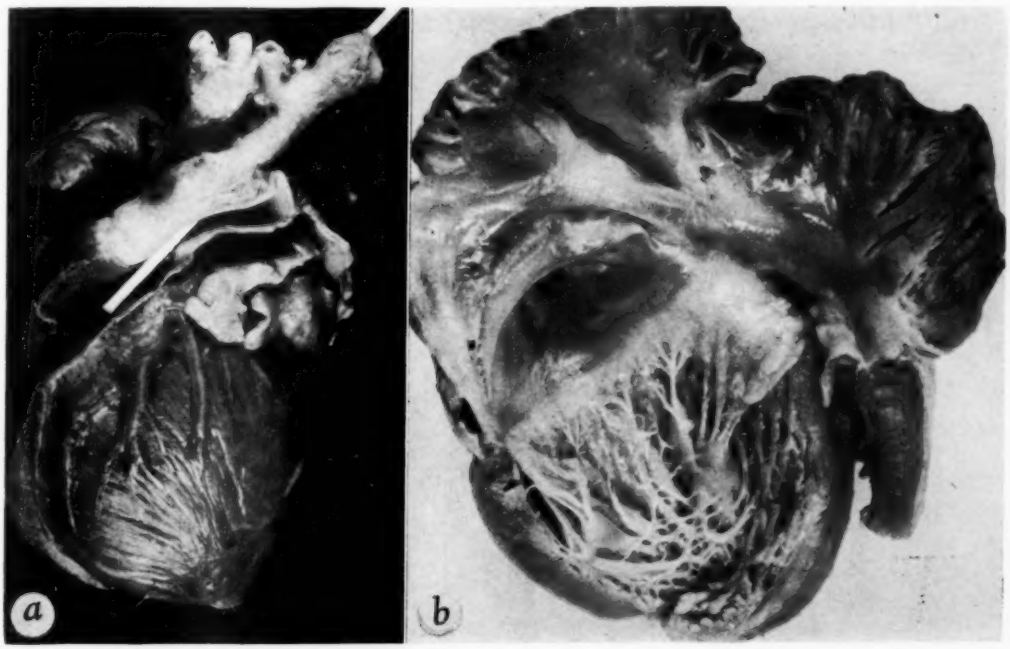

Fig 4 (Case 6).—Cor triloculare biatriatum without transposition of the great vessels (type 2). *a*, Exterior of heart showing normal relationship between the great vessels. A probe placed in the patent ductus arteriosus emerges from the upturned end of the descending aorta. *b*, The interior of the heart viewed from the right. There is a common atrioventricular orifice and valve. The lower portion of the atrial septum is defective.

Incidence.—While cor triloculare biatriatum is an uncommon congenital cardiac anomaly, it is nevertheless observed much more frequently than cor biloculare. In each of our nine patients the heart was among 175 examples of major anomalies of this organ and the great vessels in the collection of pathologic specimens of the clinic. In 1,000 cases of congenital cardiac disease which Abbott[1] collected both from the literature and from her own experience, cor triloculare biatriatum occurred thirteen times. This should not be construed to mean that only thirteen cases had been reported up to the time of Abbott's publication, since in Bauer and Astbury's bibliography[2] of the 1,000 cases analyzed in Abbott's atlas, some of the cases cited by Young,[20] Favorite,[8] and others were not included under the heading of cor triloculare biatriatum. The interested reader will find works of others reported subsequent to the time of Abbott in the papers of Favorite,[8] Kornblum,[14] Drey and associates,[4] Herndon and co-workers,[12] Moskowitz,[17] Glendy, Glendy, and White,[10] Mehta and Hewlett,[16] Greenberg,[11] and Richman.[18]

Age.—The nine patients in our series survived from 3 weeks to 8 years. In thirteen cases collected from the literature by Abbott, the ages of patients at death ranged from birth to 35 years. The mean age at death was 7¾ years. Her series included four patients who lived to the age of 21 years or more. In the recent literature, Favorite's patient[8] lived 18½ years, Kornblum's[14] 5 months, Drey, Strauss, and Gray's[4] 14 years, Moskowitz'[17] 4 months, Herndon, Vass, and Donovan's[12] 49 years, Glendy, Glendy, and White's[10] 9 years, Mehta and Hewlett's[16] 56 years, Greenberg's[11] 6 years, and Richman's[18] 4 days. The survival rate for cases reported in the literature is considerably higher than that for our patients. It is conceivable that the stimulus to report cases of patients who survived an unusually long time is greater than that to report cases of patients dying in early infancy and childhood; consequently, a truer picture of the over-all survival would be obtained from a study of reports of several authors who included all patients they had observed rather than from a study of reports of isolated cases.

Fig. 5 (Case 7).—Cor triloculare biatriatum. The great vessels are transposed. Between the origin of the left common carotid artery (*L. C. C.*) and the origin of the left subclavian artery (*L. S. A.*) tubular hypoplasia of the aortic arch can be noted. The ductus arteriosus (*D. A.*) runs between the left pulmonary artery and the descending aorta.

Cyanosis.—In Case 1 cyanosis, which was present at birth, was mild until shortly before death at 10 months of age. In Case 2 only slight cyanosis was observed prior to development of a fatal cerebral abscess at the age of 6 years.* The third patient had slight cyanosis from birth. In Case 4 cyanosis was not present until the patient was 7 months of age. Case 5 was characterized only by terminal cyanosis at 5 months. In Cases 6 and 7 mild cyanosis was reported during the three weeks of life of each patient. In Case 8 moderate cyanosis was reported during the three years of the patient's life. The ninth patient was characterized by cyanosis during his eight years of life.

*This case was reported in an earlier paper.[9]

A summary of these observations showed that cyanosis was not apparent during the first seven months of one patient's life and that cyanosis was mild in two patients until shortly before death. In the remaining six patients, mild or moderate cyanosis was present during the entire life of each; the ages varied from 3 weeks to 8 years.

The absence of severe cyanosis in all of our patients with cor triloculare biatriatum, in spite of the free mixture of blood in a common ventricle, may undoubtedly be correlated with the fact that none of the patients had severe pulmonary stenosis or atresia and consequently had adequate pulmonary blood flow. The possibility of absence of cyanosis in association with cor triloculare biatriatum was emphasized in cases reported in the literature. Of particular interest is the case reported by Young[20] and also by Mann[15] of a man, 35 years of age, who apparently did not have cyanosis until three weeks before his death. Necropsy revealed a common ventricle with transposition of the great vessels. Pulmonary stenosis was not present.

Persistent cyanosis was observed in the case recorded by Favorite.[8] Cyanosis was present only at birth and at death in Kornblum's[14] case of an infant, 5 months of age.

In the case of a girl, 14 years of age, reported by Drey, Strauss, and Gray[4] cyanosis was persistent from the time of birth. This feature might be correlated with the relatively narrow opening between the main part of the common ventricle and the outlet pocket of the ventricle from which the pulmonary trunk arose. In the case of Herndon, Vass, and Donovan,[12] which concerned a man who lived to be 49 years of age, cyanosis was never a prominent feature. Glendy, Glendy, and White[10] reported the case of a patient, 9 years of age, whose condition was diagnosed clinically as rheumatic cardiac disease because of systolic and diastolic murmurs and absence of cyanosis. Necropsy revealed cor triloculare biatriatum. The patient of Mehta and Hewlett[16] was a woman, 56 years of age, with cor triloculare biatriatum, who showed evidence of persistent cyanosis and polycythemia. Necropsy revealed the absence of the pulmonary trunk. The source of the pulmonary blood was a branch of the innominate artery. In this patient it is probable that the vessel carrying blood to the lungs was inadequate to carry a full complement of pulmonary blood, and its inadequacy was probably responsible for the persistent cyanosis.

Murmurs.—Records of physical examinations were available for eight of our nine patients. A child, 2½ months of age (Case 3), who had had mild cyanosis from birth, died during a spell of vomiting before medical aid could be summoned.

In seven of the remaining eight patients a systolic cardiac murmur was exhibited: In three the murmur was described as being heard over the entire precordium; in three a systolic murmur was heard with greatest intensity over the second and third left intercostal spaces at the sternal margin; and in one (Case 4) the murmur was loudest over the right side of the precordium. In the latter patient, isolated dextrocardia existed.* In two patients a thrill accompanied the systolic murmur.

*This case was reported in an earlier paper.[5]

In Abbott's thirteen patients, a systolic murmur was recorded in five instances, and in a sixth there was a continuous murmur. Systolic murmurs were also recorded for the patients of Favorite, Kornblum, Drey, Strauss, and Gray, Mehta and Hewlett, and Herndon, Vass, and Donovan. The systolic and diastolic murmurs in the patient of Glendy, Glendy, and White have already been mentioned. A to-and-fro murmur was reported in the patient of Moskowitz.

It is evident that a systolic murmur is commonly associated with cor triloculare biatriatum, such a murmur having been present in all of our patients on whom physical examinations had been done. Likewise, a similar murmur was described in most of the cases reported in the literature. Occasionally, a diastolic murmur also was present.

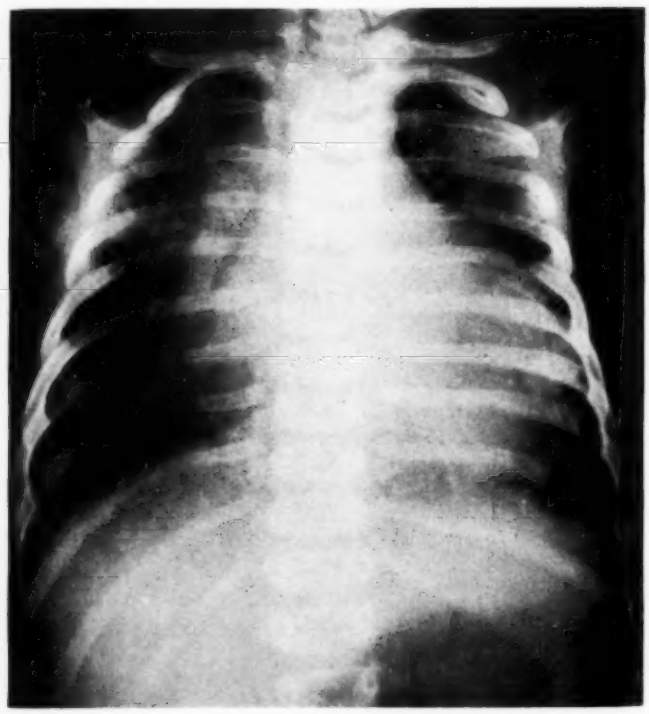

Fig. 6 (Case 5).—Cardiac enlargement is evident in this roentgenogram of the thorax of a 5-month-old baby girl with cor triloculare biatriatum, type 1A.

Electrocardiograms.—For four of our patients electrocardiograms had been taken. In two instances (Cases 2 and 9) right axis deviation was present. In two patients (Cases 4 and 5) left axis deviation was present. The presence of left axis deviation is an important point in patients in whom cyanosis may be present, since it is usually accepted that this type of electrocardiographic tracing for a patient with congenital cyanotic cardiac disease is strong evidence in favor of tricuspid atresia. Richman observed that the electrocardiographic patterns of a newborn infant having cor triloculare biatriatum were similar to those of a normal infant of comparable age.

Roentgenograms.—Evidence of cardiac enlargement was present in each of the four patients of whom roentgenograms of the thorax were made (Fig. 6). In one patient (Case 4) isolated dextrocardia was evident. These findings were substantiated pathologically. The hearts of all patients were profoundly enlarged in comparison to those with normal weight.

SUMMARY

Nine cases of cor triloculare biatriatum, which represent all cases of this anomaly in the collection of pathologic specimens in the Mayo Clinic, are reviewed pathologically and clinically.

In eight patients there was associated transposition of the great vessels. In six of these, the outflow tract of the common ventricle was so divided as to create a narrow tract leading to the aorta. The pulmonary trunk was wide. In the other two patients, a subpulmonary fibrous collar created a moderate degree of subpulmonary stenosis.

The ninth patient (Case 6) was unusual in that the great vessels were not transposed.

Coarctation of the aorta was associated with cor triloculare biatriatum in two patients. In one of these, tubular hypoplasia of the aortic arch between the left common carotid and left subclavian arteries also was present. In still another patient, this aortic abnormality existed but without associated coarctation.

Six of the nine patients were male, and three were female. The age at death varied from 3 weeks to 8 years. Records of physical examination were available for seven patients, and each showed the presence of a precordial systolic murmur. At times, this was associated with a precordial thrill. Cyanosis varied in degree. In one instance, it was not recognized until the patient was 7 months of age. In several instances, cyanosis was mild and became intensified only before the patient's death. Mongolism was associated with cor triloculare biatriatum in one patient, and isolated dextrocardia occurred in one patient. Electrocardiographic examination revealed right axis deviation in two patients and left axis deviation in two.

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Clinical Reports

AN UNUSUAL CASE OF PAROXYSMAL AURICULAR FIBRILLATION DUE TO MEDIASTINAL MALIGNANT LYMPHOMA

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NEW YORK, N. Y.

IN 1942, Scott[1] reported a case of paroxysmal auricular flutter and fibrillation with metastatic carcinoma of the left auricle. Herein is reported a case of paroxysmal auricular fibrillation due to the extrinsic pressure of a mediastinal tumor, successfully treated by x-ray.

CASE REPORT

The patient was a 63-year-old white woman who complained of frequent episodes of palpitation and dyspnea and a sense of "shaking" of the entire left thoracic cage during the episodes. During one attack, in spite of the sensation of palpitation, the patient stated her pulse was only 30 per minute.

The first attack of palpitation and shortness of breath occurred on Jan. 30, 1948, at which time there were no significant physical findings; the pulse rate was 100, and an electrocardiogram was normal. During succeeding visits to the office, there were occasional complaints of palpitation, sometimes accompanied by a sensation of shaking of the entire left chest. An electrocardiogram on March 29, 1948 (Fig. 1) was normal. A portable electrocardiogram taken during one of the episodes on April 26, 1948 (Fig. 2) revealed the presence of auricular fibrillation. At this time the pulse rate was 70, the blood pressure 140 mm. Hg systolic and 80 mm. Hg diastolic and the heart otherwise normal. The patient was placed on increasing doses of quinidine sulfate with return of rhythm to normal. She continued well until May 4, 1948, when another paroxysm occurred, lasting three hours, which was temporarily controlled by quinidine sulfate. She was then given a maintenance dose of 15 grains daily. However, the episodes of palpitation continued with increasing frequency and severity, and the patient was hospitalized for further study on June 6, 1948.

On admission to the hospital, the physical examination was again essentially normal except for a palpable lymph node in the left inferior cervical triangle. The heart sounds were normal; there was regular sinus rhythm; there was no cardiac enlargement; no murmurs were heard. The lungs were clear to percussion and auscultation. The abdomen was soft with no palpable masses or organs. An electrocardiogram on June 7, 1948 revealed regular sinus rhythm, normal atrioventricular conduction time and left axis deviation, M-shaped QRS_3, but no other abnormalities.

A roentgenogram of the chest revealed a clearly defined nodular mass (Fig. 3) in the left mediastinum in the region of the pulmonary outlet.

A bronchoscopic examination was done which revealed a thickening of the mucosa of the right bronchus on the medial side, a constriction of the opening of the superior bronchopulmonary segment, and a thickening of the opening of the lower lobe bronchus. The lower surface of the

Received for publication June 23, 1950.

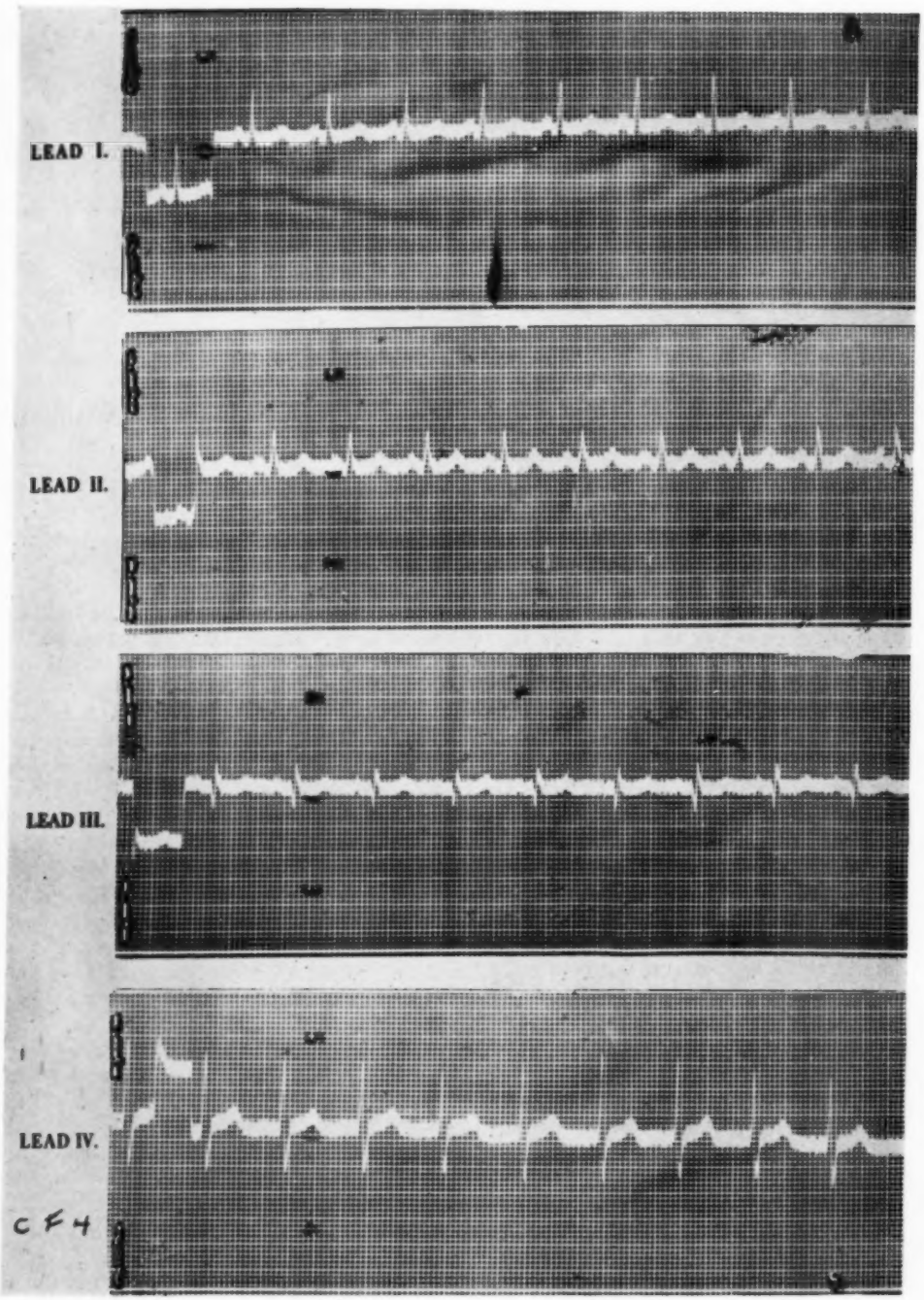

Fig. 1.—Normal electrocardiogram taken on March 29, 1948, after onset of palpitation but between attacks.

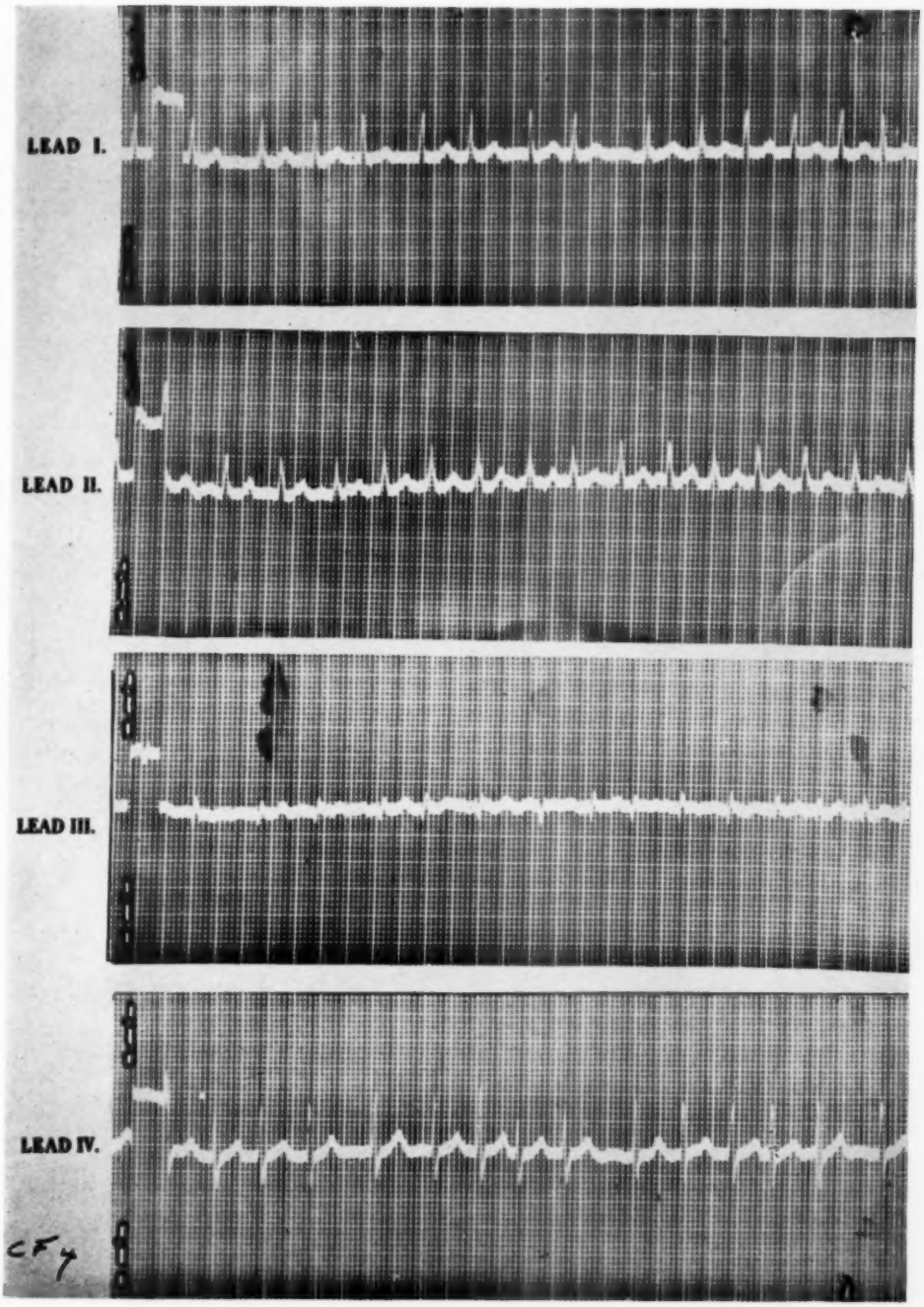

Fig. 2.—Electrocardiogram taken on April 26, 1948, during the attack of palpitation, showing auricular fibrillation.

left bronchus was thickened and narrowed, but the upper left bronchus was not seen. A biopsy was taken from the lower wall of the left bronchus and medial wall of the right bronchus, but it proved to be free of neoplastic tissue. Cultures were normal.

A history of a previous cervical gland biopsy was obtained which was done on June 8, 1946. The pathological report at that time was as follows: "Specimen consists of a firm grayish-yellow and brown, partly encapsulated nodule, measuring 1.8 cm. in diameter. Microscopic examination shows a lymph node which is packed with rather deeply staining masses of lymphocytes, which

Fig. 3.—Roentgenogram of chest taken on June 8, 1948, showing a nodular mass in the left mediastinum in the region of the pulmonary outlet.

Fig. 4.—Roentgenogram of the chest taken on Aug. 8, 1948, showing marked regression of the mediastinal mass following x-ray therapy.

show slight variation in size; there are scattered hemorrhages. Most of the architecture of the gland is destroyed and a few trabecular fibers and portions of the capsule remain. The latter shows invasion by lymphocytes." The pathological diagnosis was lymphoma of low grade malignancy.

During hospitalization, it was discovered that paroxysmal auricular fibrillation occurred when the patient would lie on the left side or would assume the erect posture. However, this arrhythmia could be prevented by the patient lying on her right side more effectively than by the use of quinidine or digoxin.

Although the bronchoscopic examination was negative, in view of the previous history of malignant lymphoma we concluded that the mediastinal tumor was a lymphoma, and x-ray therapy was started. The episodes of arrhythmia continued but slowly became more infrequent, finally disappearing within about ten weeks after the start of x-ray therapy; they have not recurred to date. A chest film taken on July 5, 1948 showed some reduction in the size of the mediastinal density in the left hilum, indicating a favorable response to x-ray therapy. Another film taken on July 20, 1948 showed still further regression, but some infiltration was noted in the left lower lobe area. For a short period during this time, the patient became febrile, and x-ray therapy was delayed for several days, then renewed again. Improvement continued, and x-ray examination on Aug. 8, 1948 showed marked regression of the mediastinal mass (Fig. 4). Clinically there was no return of auricular fibrillation, and the patient was able to return home and eventually return to work.

The patient continued well, but on Oct. 8, 1948, she noticed a swelling of the vulva. A roentgenogram of the chest was still clear, and films of the skull and orbit were normal. The blood pressure was 150 mm. Hg systolic and 80 mm. Hg diastolic; the pulse rate was 84 per minute and regular. On Oct. 22, 1948, a partial vulvectomy was done, revealing microscopic evidence of lymphosarcoma.

On re-examination, Aug. 8, 1949, the patient was found to be in good condition. She had been working for six months and had had no further palpitation, tachycardia, or gross evidence of a tumor. A roentgenogram of the chest taken on Aug. 8, 1949 revealed no evidence of the mediastinal tumor.

SUMMARY

This patient presented an unusual case of paroxysmal auricular fibrillation which was extracardiac in origin, due to extrinsic pressure, probably on the left auricle. The unusual features of postural precipitation of the fibrillation and the response to roentgen therapy are noteworthy.

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ARTERIOVENOUS ANEURYSM OF A BRANCH OF THE PULMONARY ARTERY

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ARTERIOVENOUS aneurysm of branches of the pulmonary artery is uncommon; only eight cases had been reported in the literature up to July, 1947. All of these were congenital in origin and showed polycythemia and cyanosis. Bierwalter and Byron[1] reported the first patient treated by lobectomy. Elkin and Warren[2] reported 375 soldiers with traumatic arteriovenous fistula involving every blood vessel, although no specific mention was made of the pulmonary vessels. Deterling and Clagett[3] have reported an aneurysm of the pulmonary artery (no venous connection) proved by necropsy in thirty-six cases collected from the literature.

The etiology of vascular aneurysms comprises: (1) syphilis, (2) congenital defects, (3) mycotic degeneration of the wall of the artery, (4) atheroma, and (5) trauma. These five causes explain arterial aneurysms; they may be similar for arteriovenous pulmonary aneurysms, although Liebow[5] believes they are all congenital in origin.

CASE REPORT

As the result of a routine industrial and community x-ray survey by the Connecticut State Tuberculosis Commission in October, 1949, a 56-year-old man was referred to his physician. A posteroanterior 4 by 5 inch stereoscopic film of the chest showed a round shadow of hard density, measuring 1.3 cm. in diameter, in the central zone of the right lung, below the tenth rib posteriorly. The border of this shadow was sharply defined, and there were no visible changes in the adjacent pulmonary tissues.

A single 14 by 17 inch posteroanterior film of the chest, taken for the follow-up unit of the Connecticut State Tuberculosis Commission on Jan. 26, 1950, revealed a large, solitary, round, homogeneous shadow of medium density in the right mid-lung zone, just above the diaphragm, partially obscured by the tenth posterior and sixth anterior ribs. The shadow seen was sharply defined and was 3.8 cm. in diameter. A lateral film localized this slightly anteriorly, and there was a broad, fairly well-defined, linear shadow of medium density extending from the round shadow previously described to the hilar area.

Impression.—It is felt that the shadow described above represented in all probability a bronchial cyst. The possibility of a tumor mass, malignant or nonmalignant, could not be disregarded. It was localized in lateral films, probably in the lower posterior portion of the middle lobe of the right lung.

The patient had been previously x-rayed by the Connecticut State Tuberculosis Commission on Feb. 5, 1948, and May 3, 1944, and no change could be seen in the x-ray appearance.

History.—The patient is a 56-year-old man, height 5 feet, 8 inches, weight 172 pounds, with no complaints referable to his chest. He had been treated several times for severe nosebleed.

Received for publication July 3, 1950.

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In 1947, he was treated for right sciatic neuritis and, in 1949, for acute low back sprain involving lumbosacral and right sacroiliac joints. His wife and son are living and well; two brothers also are living and well. His mother died at the age of 83 years of vaginal hemorrhage. His father died many years ago; the cause is unknown.

The physical and laboratory examinations were entirely normal except for a to-and-fro continuous murmur heard in the right anterior axillary line from the lower border of the lowest rib to the nipple.

Laboratory Tests.—On April 10, 1950, the serological tests showed the following: Mazzini, 4+; Eagle and Hinton, positive; Kolmer and Connecticut fixation, negative; and Kahn, 4+. In his last industrial record, April 5, 1946, the following serological test results were found: Kahn standard, doubtful 1+; Kolmer, negative; Kline diagnostic, ± doubtful; Kline exclusive, positive 2+; and Mazzini, doubtful 1+. In 1943, a Mazzini test was doubtful.

Fig. 1.—Described in text.

About 8 c.c. of clear, colorless spinal fluid were obtained in three tubes. There was no pellicle. The cell count was 1 per cubic millimeter (1 lymphocyte and 3 red cells); total protein, 30 mg.; sugar, 75 mg.; and colloidal gold, 0000000000. An electrocardiogram was essentially normal except for a small Q_2 and Q_3.

With the detection of the bruit, the patient was x-rayed* with a particular request for lateral and oblique views and fluoroscopy. The report was as follows: Examination of the chest by fluoroscopy, spot films, and stereoscopic posteroanterior views revealed a rounded mass of 3.5 by 4.7 cm. as projected in the anterior portion of the right middle lobe. There seemed to be a large vessel leading to the mass, and a large vessel of more tortuous character leading toward the hilus from the mass (Fig. 1). Calcific deposits were seen in the wall of the mass. Fluoroscopic and film signs favored the diagnosis of arteriovenous aneurysm. The heart was not enlarged. The transverse diameter was 13.9 cm. The contour of the heart suggested the possibility of a slight relative prominence of the right ventricle.

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COMMENT

Arteriovenous aneurysm of a branch of the pulmonary artery was not diagnosed by several physicians who saw the patient. This was true of congenital pulmonary arteriovenous aneurysm as reported by Bierwalter and Byron.[1] The failure in diagnosis is due to not appreciating its possible presence and to not listening for the bruit.

SUMMARY

A case of pulmonary arteriovenous aneurysm is presented. Whether it is congenital or syphilitic in origin has not been determined. The case is reported as it is an unusual lesion and may be amenable to antisyphilitic treatment and/or lobectomy.

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AN UNUSUAL RESPONSE TO CAROTID SINUS PRESSURE

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IT IS well known that cardiac action may be influenced by autonomic reflexes; vagus reflexes elicited by carotid sinus pressure, ocular pressure, the Valsalva experiment, and other mechanisms are widely used to abolish attacks of paroxysmal tachycardia.

In rare instances paradoxical reactions are obtained by such measures. They do not abolish an attack, rather they elicit one. Since such observations are still scarce we feel justified in reporting a case in which carotid pressure led to the appearance of a paroxysmal auricular tachycardia. To our knowledge, no other case of this type has been reported.

CASE REPORT

A 73-year-old white man was admitted to the hospital on Dec. 27, 1949, because of the sudden onset of "weakness" six days previously. At that time the patient stated he suddenly felt that his legs were unable to carry him, and he fell to the floor. He did not lose consciousness, but he could not get up for eight to ten hours. During that time, he had been able to move all extremities. Following this episode, he had a gradual recovery, but at the time of admission he was still unable to take care of himself. The past history revealed exertional dyspnea of four to five years' duration. The patient also described occasional episodes of "craziness of the heart" which frequently he was able to stop by deep inspiration and elevation of the arms.

Physical examination revealed an elderly man appearing chronically ill. The pertinent findings were those of generalized arteriosclerosis, as evidenced by funduscopic examination, and lack of pulsations in the peripheral arteries of both lower extremities. The blood pressure was 140/85 mm. Hg, and the pulse was 80 per minute. The heart sounds were normal; no murmurs were heard. A chest roentgenogram showed the heart to be essentially normal in size and shape. The aorta was dilated and tortuous with a prominent knob. The electrocardiogram showed a sinus rhythm of 84 with a P-R interval of 0.20 second. The patient was treated with papaverine hydrochloride and Priscoline, and a paravertebral block with procaine was performed. No improvement was noted after these measures.

On the tenth hospital day, while out of bed, the patient suddenly developed a sensation of tightness in the chest. Apical and radial pulsations amounted to 150 per minute, and an electrocardiogram taken a few minutes later revealed the presence of a supraventricular tachycardia. Fig. 1,*A* (Lead II) shows the effect of carotid pressure performed on the left side. It can be seen that during the carotid pressure the tachycardia disappeared promptly. After a few atrioventricular beats, sinus rhythm reappeared with a P-R interval of 0.24 second and a rate of 115.

A few minutes later, carotid pressure was again applied on the left side (Fig. 1,*B*). A cardiac standstill lasting about 4 seconds resulted. It was terminated by an escaped beat presumably of an atrioventricular nodal origin, and this was followed by the reappearance of the paroxysmal

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Received for publication July 19, 1950.

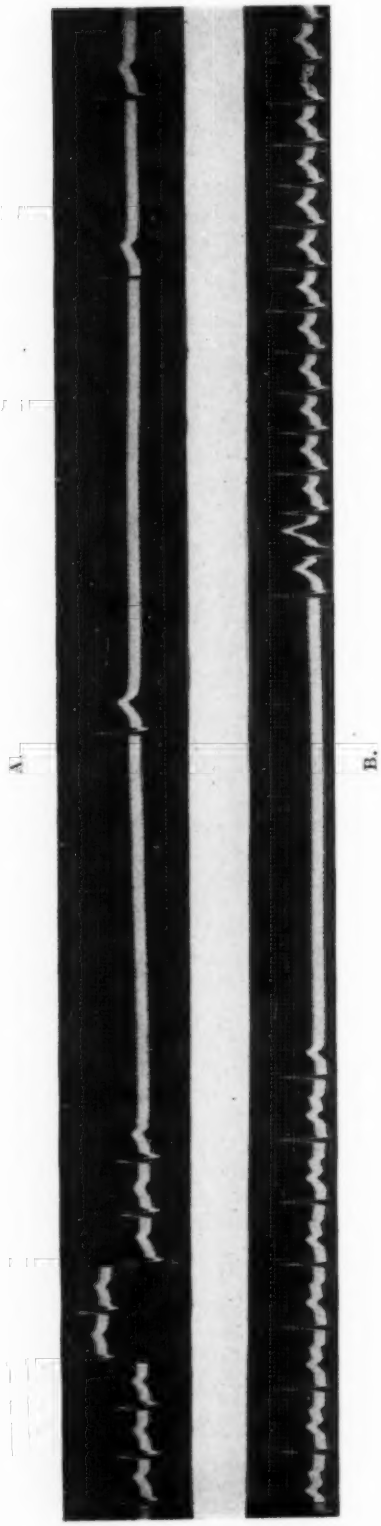

Fig. 1.—*A*, Paroxysmal auricular tachycardia terminated by carotid sinus pressure. *B*, Paroxysmal auricular tachycardia caused by carotid sinus pressure.

tachycardia with an aberrant conduction of the first abnormal beat. The higher T wave of the escaped beat was presumably caused by a superimposed P wave, demonstrating an auricular origin of the tachycardia.

It was possible during other spontaneous attacks of paroxysmal tachycardia to stop the attack immediately by carotid pressure, but we never succeeded again in eliciting these attacks by the same measure. The patient learned to stop the attacks himself by carotid pressure.

DISCUSSION

The unusual feature of this case was the appearance of supraventricular paroxysmal tachycardia during carotid pressure, while this same measure had abolished a similar attack in the same patient a few minutes before.

While to our knowledge, no case of paroxysmal auricular tachycardia caused by carotid pressure has been published, the appearance of other arrhythmias by such a maneuver has been known to occur.

In the classic work on cardiac arrhythmias by Wenckebach and Winterberg,[10] a case of paroxysmal ventricular tachycardia was reported in which it was possible to elicit such paroxysms by carotid sinus pressure. The patient was a 55-year-old, emotionally distraught woman who began to have nightly attacks of severe palpitation lasting up to two hours. The physical examination revealed a nervous, otherwise healthy, woman; the heart was normal. The blood pressure was 110/70 mm. Hg. The electrocardiogram before the attack showed normal sinus rhythm with left axis deviation. After right carotid pressure, there was first a cardiac standstill of 2.2 seconds. This was followed by a supraventricular beat, then by a group of five premature beats originating from the right ventricle. After an interval of 1.08 seconds and preceded by another supraventricular beat, there was a continuous sequence of premature beats originating from the right ventricle, the second of these showing aberrant conduction, as in the case presented in this paper.

After the attack had lasted fifteen to twenty minutes, right carotid pressure was applied again, and the attack stopped immediately. The same experiment could be performed repeatedly.

Recently, two cases were reported[4] in which short attacks of paroxysmal ventricular tachycardia were elicited by carotid sinus pressure in an attempt to stop pre-existent paroxysmal supraventricular tachycardia.

It has been well established experimentally and clinically that stimuli along the entire respiratory tract may produce cardiac standstill, bradycardia, extrasystoles, and paroxysmal tachycardias.[8] These observations have been attributed to cardiorespiratory and pulmonocardiac reflexes whose afferent fibers arise in the lining of the respiratory tract from the nasopharynx to the alveoli and also in the intrapulmonary blood vessels. These reflexes, supposedly by increasing vagal tonus, could account for the cardiac effects of intratracheal intubation, pulmonary surgery, pulmonary embolism, and so forth. The reported cases of paroxysms of premature contractions and auricular fibrillation either produced or abolished by deep breathing are presumably on the same basis.[9]

Numerous cases have been reported in which attacks of paroxysmal tachycardias and other transient cardiac effects were elicited by swallowing.[1,3,6]

Forssman and Stenquist observed a particularly interesting patient who was able to produce a paroxysmal tachycardia by swallowing and also by deep inspiration or the performance of the Valsalva maneuver.[2]

Experimentally, Piccione and Scherf caused paroxysmal attacks of ventricular tachycardia by application of barium chloride or sodium chloride to the ventricular surface of the dog's heart.[5] Vagus stimulation brought such attacks out again after they had disappeared. Fig. 6 of these authors shows a striking resemblance to our Fig. 1,*B*.

Similarly, it may be noted here that drugs which cause extrasystoles may also abolish them. Extrasystoles may develop in a damaged heart muscle following therapy with digitalis, and in such cases great caution should be exercised before administering further doses. Extrasystoles, however, which appear in normal subjects or cardiac patients without digitalis treatment are no contraindication to the drug, which may abolish them completely.

It is interesting to note that the second QRS complex of the attack of paroxysmal tachycardia in Fig. 1,*B* differs from the rest. This abnormal conduction of the second impulse in a series of regularly conducted impulses appearing after a long pause was investigated by Scherf. The explanation offered was that the first impulse appearing after a long pause is followed by a particularly prolonged refractory period so that the subsequent impulse finds the conduction tissue in a less favorable state of recovery.[7]

SUMMARY

A case is reported in which carotid pressure precipitated an attack of paroxysmal auricular tachycardia. The same measure abolished readily spontaneous attacks.

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